



update

Winter
Volume 24, Issue 2, 2013
News and Views

Radiation Effects Research Foundation Hiroshima and Nagasaki, Japan



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

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

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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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From the Editors

Welcome to the second issue of *RERF Update* for 2013. It is late November in Japan, and the chilly weather has finally taken hold as temperatures have suddenly declined to seasonally typical values in the last week, after a very mild early autumn. The Yebisu Festival (Yebisu is a Japanese god of good fortune and guardian of the ocean, fishing folk, and business prosperity) is in full swing in downtown Hiroshima including Chuodori, one of the city's main streets, and the extensive seasonal lighting display along Peace Boulevard, which has grown both in scale and popularity in recent years with the advent of LED lighting, has returned in even greater profusion than last year.

This has been a time of changes in staff, with the eagerly awaited arrival of our new Associate Chief of Research, Dr. Robert Ullrich, whose self-introduction appears in this issue, along with thoughts on retirement by Dr. Masazumi Akahoshi, Chief of the Clinical Studies Department in Nagasaki, and self-introductions by a new researcher in Statistics, Dr. Reid Landes, and a new fellow in Epidemiology, Ms. Caitlin Milder. We bring you the usual reporting on important events, including the annual Open House, information on an award received by one of our researchers, Dr. Hiromi Sugiyama of Epidemiology, and reports on several workshops and meetings. We have a number of science articles about current research taking place at RERF, along with a report on the program in which RERF clinicians and other staff participate in health examinations for A-bomb survivors living in North America. RERF Chairman Dr. Toshiteru Okubo has contributed a "Facts and Figures" piece on the completion of a multi-year project at RERF that has as its aim the improvement of survivors' dose estimates by combining new technology and



Editor-in-Chief Harry Cullings (front, left), alongside Kotaro Ozasa, Chief, Department of Epidemiology, speaking at a press conference on leukemia and other cancers among A-bomb survivors (please refer to page 15)

computer-based methods with archival materials on survivors' locations at the times of the bombings to improve the estimates of their map coordinates.

We hope that you will enjoy this winter issue as we approach the year-end holidays and the time for another *bonenkai* (a party to reminisce about, and send off, the year about to end)!

Harry M. Cullings
Editor-in-Chief

Fumie Maruyama
Technical Editor

Third Board of Councilors Meeting Held at the Hiroshima Laboratory

The third meeting of the Board of Councilors (BOC) was held at RERF's Hiroshima Laboratory over the two days of June 18 and 19, 2013. All Councilors as well as Directors, Auditors, and the Japanese Co-chair of the Scientific Advisory Committee (SAC) attended the meeting. Officials of the U.S. and Japanese governments, the U.S. Embassy in Tokyo, and the National Academy of Sciences (NAS) participated in the meeting as observers. At the beginning of the meeting, the representatives of the two governments gave greetings, expressing

their commitment to providing continued support to RERF. The following is a summary of the meeting's proceedings.

Several reports were made for FY2012—an activities report, settlement of accounts report, and audit report—with the settlement of accounts report approved as presented. The Councilors raised questions and commented on the activities report including issues such as RERF's future plans, Biosample Center, and "black rain" exposure data.

As was done last fiscal year, reports also were made about the major activity plans for FY2013, including research projects related to the health of A-bomb survivors and their children, projects aiming at revisions of individual radiation doses and the effects on risk calculations from such revisions, the public release of research results, collaborations with other scientific organizations, training programs for Japanese and overseas specialists, public information programs, and plans and budget estimates necessary to conduct these major activities. Plans for further development of the Biosample Center, established in April 2013, were also presented.

Dr. Shunichi Yamashita, the Japanese SAC Co-chair, reported on the recommendations made by the SAC at its 40th meeting (held March 4–6, 2013, at the Hiroshima Laboratory), the focus of which was the SAC's review of the activities of RERF's Department of Clinical Studies. Dr. Yamashita reported that the SAC's general recommendations included calls for further improvement of RERF's research quality, serious consideration to be paid to prioritization of research projects, development of future plans for the reorganization of RERF's research structure and for the nurturing of its human resources, as well as enhancement of RERF's global impact and social contributions. RERF's responses to these recommendations were presented and discussed. RERF's efforts toward establishment of the Biosample Center with a view to developing a system for more efficient storage and use of research samples were commended.

The Rules of Procedure of the Board of Councilors were established last year, and appointments were made in accordance with the rules for the first time at this meeting. Two Councilors, three Directors, three Scientific Advisors, and two Local Advisors were appointed or reappointed.

Lastly, a decision was made to hold next year's BOC meeting and its informal executive session at the Nagasaki Laboratory.

List of Participants

Councilors:

- Mr. Masaaki Kuniyasu**, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal
- Dr. Yasuhito Sasaki**, Special Advisor, Oncology Center, Hidaka Hospital
- Dr. Hiroo Dohy**, Director, Japanese Red Cross Chugoku-Shikoku Block Blood Center
- Dr. Ohtsura Niwa**, Professor Emeritus, Kyoto University
- Dr. James D. Cox**, Former Head, Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center

Dr. Shelley A. Hearne, Visiting Professor, Johns Hopkins Bloomberg School of Public Health, Department of Health Policy and Management

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine; and Director, Institute for Global Health, University of Southern California

Mr. James W. Ziglar, Senior Counsel, Van Ness Feldman, and Senior Fellow and Advisor to the Board, Migration Policy Institute (Former Sergeant at Arms of the United States Senate)

Directors:

Dr. Toshiteru Okubo, Chairman/Representative Director

Dr. Roy E. Shore, Vice Chairman and Executive Director

Mr. Takanobu Teramoto, Executive Director

Auditors:

Mr. Takashi Kohno, Hiroshima General Law/Accounting Office (Hiroshima CPA Cooperative Office/A&A Tax Accountant Corporation)

Mr. David Williams, Senior Financial Advisor, National Academy of Sciences

Co-chair of Scientific Advisory Committee:

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

Representatives of Supporting Agencies:

Mr. Takeshi Sakakibara, Director, A-Bomb Survivor Support Office, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW)

Dr. Shuichiro Hayashi, Deputy Director, General Affairs Division, Health Service Bureau, MHLW

Mr. Hiromasa Kuroki, Deputy Director, A-Bomb Survivor Support Office, General Affairs Division, Health Service Bureau, MHLW

Mr. Glenn S. Podonsky, Chief Health, Safety and Security Officer, Office of Health, Safety and Security, U.S. Department of Energy (DOE)

Dr. Patricia R. Worthington, Director, Office of Health and Safety, Office of Health, Safety and Security, DOE

Dr. Isaf Al-Nabulsi, Japan Program Manager, Senior Technical Advisor, Office of Health and Safety, Office of Health, Safety and Security, DOE

Mr. Dean C. Hickman, Special Advisor, Office of Health, Safety and Security, DOE

Mr. Jeffrey Miller, Energy Attaché and Director, DOE Tokyo Office

Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life

Studies, National Research Council, U.S.
National Academy of Sciences

RERF:

Dr. Kazunori Kodama, Chief Scientist

Mr. Eiji Akimoto, Chief of Secretariat

Mr. Douglas C. Solvie, Associate Chief of Secretariat

Mr. Yutaka Ogasawara, Associate Chief of Secretariat



Participants of the third Board of Councilors meeting held at Hiroshima RERF

Nagasaki RERF Holds Third Public Lecture Event for Citizens

RERF held its third public lecture event for Nagasaki citizens at the Nagasaki A-bomb Museum Hall, from 1:30 to 4:00 in the afternoon of June 29 (Sat.). This open lecture series is carried out to promote exchange between RERF staff and the general public including A-bomb survivors, by providing clear explanations about results and findings from RERF's longstanding research into A-bomb radiation health effects. More than 120 people attended the most recent event.

At the beginning of the public event, following greetings by Chairman Toshiteru Okubo, Mr. Sumiteru Taniguchi, President of the Nagasaki Atomic Bomb Survivors Council, shared with the audience his memories from the time of the bombing of that city. He also expressed his expectations for RERF's continued cooperation and support.

The event consisted of two lectures. First, Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, spoke on "Physical changes induced by radiation exposure: Cancer development and immune alterations," explaining various possible mechanisms of radiation-induced disease development and the significance of elucidation of such mechanisms, information that is expected to enable accurate estimation of disease risks as well as effective disease prevention and treatment. Next, Dr. Ayumi Hida, Assistant Chief,

Nagasaki Department of Clinical Studies, gave a lecture titled "Findings from the long-term health-examination program for A-bomb survivors," introducing findings obtained from the Adult Health Study conducted over many years in language appropriate for the layperson. She also expressed her gratitude to the A-bomb survivors for their cooperation in the study and asked for their continued participation and support.

In the special remarks session after the two lectures, Dr. Takehiko Koji, Dean of the Nagasaki University Graduate School of Biomedical Sci-



Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, speaking at the third public lecture for citizens in Nagasaki

ences, provided his feedback on the lectures and talked about the roles to be played by RERF in the future. The question-and-answer session that followed was marked by many questions showing

a strong interest in health damages from radiation exposure in general and other such issues, as well as those originating from audience members anxious about their own health.

Local Liaison Council Meetings Held at Hiroshima and Nagasaki

The 19th meeting of the Hiroshima Local Liaison Council (HLLC) was held at Hiroshima RERF on September 9, 2013. Of the 15 Council members, 14 (including one proxy) attended the meeting and expressed many valuable opinions.

After the introduction of Council members by Mr. Eiji Akimoto, RERF Chief of Secretariat, RERF Chairman Toshiteru Okubo, in his opening remarks, explained the objectives of establishment of the liaison council. After greetings by HLLC Chairman Dr. Toshimasa Asahara (President of Hiroshima University), the meeting's proceedings began, with Dr. Okubo touching on RERF's present status, followed by reports made by Vice Chairman and Executive Director Roy E. Shore on recent progress in research, Chief Scientist Kazunori Kodama on establishment of the RERF Biosample Center, Dr. Okubo on progress in the collaborative study with the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and Executive Director Takanobu Teramoto on RERF's public relations activities. Each of these reports was followed by a question-and-answer session. In an exchange in one of the sessions, a Council member requested that RERF provide radiation-effects training to physicians in Hiroshima.

It also was reported that the Biosample Center, established in April 2013, was undergoing preparations for the initiation in April 2014 of integrated management of RERF's archival biosamples. To review future utilization of archival biosamples by both RERF and outside researchers, the collection of opinions from A-bomb survivors and other local residents is considered necessary, and to that end, it was announced that a panel discussion would be held on November 30, 2013, as part of RERF's series of public lectures.

The 22nd meeting of the Nagasaki Local Liaison Council (NLLC) was held at Nagasaki RERF

on September 25, 2013. Of the 21 Council members, 15 (including three proxies) were in attendance. After introduction of new Council members by Mr. Akimoto and greetings by Dr. Okubo, the proceedings got underway, with NLLC Chairman Dr. Shigeru Katamine (President of Nagasaki University) presiding over the meeting. As was the case for Hiroshima, the current status of RERF and other issues were reported by RERF participants.

Each of the above reports was followed by a question-and-answer session and active debate among the Council members, including about such topics as the objectives and management of the Biosample Center, data in RERF's possession, and RERF's research achievements, resulting in the expression of many valuable opinions. Dr. Katamine concluded the 22nd NLLC meeting with closing remarks: "The objectives of this Council are to compile requests from the local community and have them reflected in RERF's operations. I hope that RERF can fully review and then utilize the comments and opinions expressed during this meeting in that way in the future."

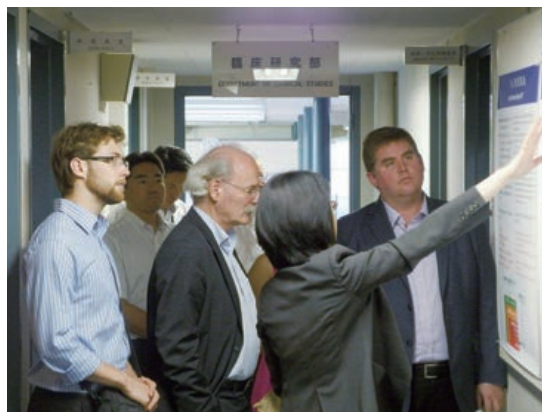


22nd Local Liaison Council meeting held at Nagasaki RERF

ICRP Vice-chair Jacques Lochard Visits RERF

Vice-chair Jacques Lochard (Committee 4 Chair) of the International Commission on Radiological Protection (ICRP), together with Scientific Secretary Chris Clement, Assistant Scientific Secretary Michiya Sasaki, and two other ICRP members, visited RERF on July 16. Staying at RERF for more than three hours, the group engaged in discussions after being briefed on the following topics: “Outline of RERF research programs and dose estimates” by Chairman Toshiteru Okubo; “Use of cancer registries, radiation and heart disease, and recent study results” by Chief Scientist Kazunori Kodama; “Risk among children” by Dr. Kotaro Ozasa, Chief of the Department of Epidemiology; and “Radiation-induced cancer and spontaneous cancer” by Dr. Yoichiro Kusunoki, Chief of the Department of Radiobiology/Molecular Epidemiology. The ICRP group was then led on a tour of RERF’s facilities by Dr. Kodama, with the department chiefs briefing the group members on each

department’s activities and research results using explanatory panels and other information.



Vice-chair Jacques Lochard (third from right) listens to explanation by Waka Ohishi (second from right), Acting Chief, Department of Clinical Studies

Senior Vice Minister Kenya Akiba of the Ministry of Health, Labour and Welfare Visits RERF

Senior Vice Minister Kenya Akiba of the Ministry of Health, Labour and Welfare visited RERF’s Hiroshima Laboratory on August 21, 2013. He spent more than one hour at RERF with three other visitors, including Mr. Hidekazu Inagawa, Chief of the Chugoku-Shikoku Regional Bureau of Health and Welfare. At the beginning of his visit, Mr. Akiba was greeted by Chairman Toshiteru Okubo, Vice Chairman Roy E. Shore, and others in the Chairman’s Office. He listened with interest to Chairman Okubo’s explanation of the history of RERF and summary of its research activities, frequently asking questions. Chairman Okubo and Executive Director Takanobu Teramoto then took Mr. Akiba on a tour of the RERF facilities, including the health examination clinic for A-bomb survivors and their children, the ABCC-RERF historical panel exhibit, and the Biosample

Center, which was established in April of this year.



Senior Vice Minister Kenya Akiba (left) listens to explanation by Toshiteru Okubo, Chairman

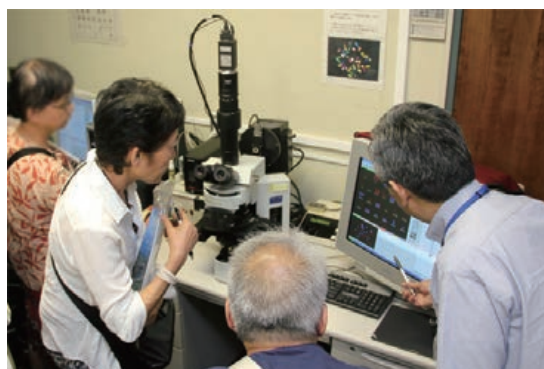
Open House 2013 Held at Hiroshima and Nagasaki

RERF's Hiroshima and Nagasaki Laboratories held their 19th and 17th Open House events under the theme "Studying and Understanding Radiation" on August 5–6 and August 8–9, 2013, respectively. Exhibits included the latest information on ongoing RERF studies, which have continued to yield results thanks to the understanding and cooperation of many people including A-bomb survivors. This year's Open House events also included a special poster exhibit titled "Considering risks from low-dose radiation exposure."

In Hiroshima, one exhibit introduced RERF public relations activities (such as open seminars for citizens, tours of the facilities, acceptance of visitors and trainees from abroad, and dispatch of lecturers). Several walking courses recommended for different objectives were established, and the installation of guide signs near the ceilings made it easier for visitors to take tours. On August 5, Mr. Yuji Yoneyama, a licensed radiation protection supervisor (General Affairs Section/Radioisotope Facility), gave a lecture titled "What is radiation?" On August 6, Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, spoke on the topic "Why does radiation induce cancer?" Both lectures were well attended,



Open House event held in Nagasaki



Open House event held in Hiroshima

and many questions were asked after the talks concluded. Despite the intense summer heat, the Hiroshima Laboratory drew 584 visitors over the event's two days, with many people having visited the RERF Open House in past years and some attending both days of the event this year. The Open House event provided an opportunity for lively communication between visitors and RERF employees.

In Nagasaki, in addition to the abovementioned special exhibit and regular exhibit introducing research methods and achievements of RERF, a featured panel exhibit titled "Nagasaki Association for Hibakushas' Medical Care (NASHIM)" introduced the Association's activities. A total of 140 elementary school children from seven after-school programs visited the Open House, and Mr. Takanobu Teramoto, RERF Executive Director, had the opportunity to speak to a group of young elementary school teachers, demonstrating that this year's Open House appealed to younger generations. A new quiz contest, introduced with the goal of persuading visitors to read our exhibits more closely by hiding the answers within the exhibit texts, proved to be popular. Despite the intense summer heat, the Nagasaki Laboratory drew 576 visitors over the event's two days.

Staff News

As of July 1, 2013, **Reid D. Landes** joined the Department of Statistics as a senior scientist, and as of October 1, **Atsuko Sadakane**, Senior Scientist, Department of Epidemiology, was promoted to Acting Chief, Laboratory of Pathology of the same department. **Robert L. Ullrich** was appointed as Associate Chief of Research, effective November

1, to succeed former Associate Chief of Research **Evan B. Douple**, who resigned at the end of December 2012.

Dr. Ullrich is recognized internationally for his groundbreaking research on mechanisms and risk of cancer development following exposure to ionizing radiation. He will work with Vice Chair-

man (Chief of Research) **Roy E. Shore** to provide scientific leadership of RERF's research programs in clinical medicine, epidemiology, genetics, and radiobiology. An important focus of Dr. Ullrich's work at RERF will be on the application of biology, genomics, and bioinformatics to advance the scientific understanding of radiation carcinogenesis in humans.

The above-mentioned two new research staff members introduce themselves below.

Robert L. Ullrich, PhD

I joined RERF on November 1, 2013, as Associate Chief of Research. After obtaining my PhD at the University of Rochester, New York, I joined Oak Ridge National Laboratory in the United States in 1974 and served as Director of that organization's Radiation Carcinogenesis Unit until 1989, when I became Vice Chair and Director of the Biology Division in the Department of Radiation Oncology at the University of Texas Medical Branch. In 2001, I joined Colorado State University as a professor and Director of the Radiological Health Science and Cancer Research Program. In 2008, I moved back to the University of Texas Medical Branch, where I served as the John Sealy Distinguished Chair in Cancer Biology, a professor and Director of the Sealy Center for Cancer Biology (SCCB), and most recently Director of the Cancer Center.

My research over many years has focused on risks and mechanisms of radiation-induced cancer. Initially, this work investigated dose-response relationships at low doses and dose rates for radiation-induced cancer in mice. Subsequently, my laboratory at the University of Texas Medical Branch developed cell and molecular approaches for the study of mechanisms in the development of mammary cancer after radiation exposure. The most recent work at that laboratory has been funded by the U.S. National Aeronautics and Space Administration (NASA) to establish a NASA specialized center of research in radiation carcinogenesis, with a focus of studying cancer risks and mechanisms of cancer development following exposure to the unique forms of radiation encountered during space travel.

I have served on a number of scientific advisory groups both in the U.S. and internationally. In the U.S., I served on committees for the National Cancer Institute (NCI), the Department of Energy (DOE), NASA, the National Council on Radiation Protection & Measurements (NCRP), and the National Academy of Sciences/National Research



Robert L. Ullrich

Council (NAS/NRC). Internationally, I have participated in advisory committees including the International Commission on Radiological Protection (ICRP), the European Commission (EC), and the International Agency for Research on Cancer (IARC).

I am a member of several scientific societies, including the American Association for Cancer Research (AACR) and the U.S. Radiation Research Society (RRS). Most recently the RRS awarded me that organization's highest honor, the Failla Award, for significant contributions to the radiological sciences.

I had visited RERF several times in the past and am excited about the opportunity to work with the many outstanding scientists here. RERF is truly an international resource.

Reid D. Landes, PhD

I joined the RERF Department of Statistics at the beginning of July 2013. Before coming to RERF, I worked in the Department of Biostatistics at the University of Arkansas for Medical Sciences (UAMS). In total, I was at UAMS for ten-and-a-half years. The first two years I was a research associate. My wife and UAMS colleagues encouraged me to return to school and obtain a PhD, so my family and I moved to Iowa, where I entered Iowa State University. For my PhD, I focused on Bayesian methods for calibration problems. Upon graduating from Iowa State in 2005, we returned to UAMS. At UAMS, I primarily worked with psychologists and psychiatrists. Some were studying addiction, some were studying the elderly, and some were studying mental health in military veterans. I also had the good opportunity to work on the Institutional Animal Care and Use Committee—a group that provides review of and guidance on animal studies. Acquaintances on this committee introduced me to certain statistical issues encountered by radiation researchers studying radiation countermeasures. Although this type of research is not a focus of RERF, the experience brought radiation research, in general, to my awareness.

I first heard of RERF when Dr. Kyoji Furukawa, who had studied with me at Iowa State, joined RERF. In late 2010, I was hoping to find a sabbatical experience, and noticed a potential opportunity with RERF. I was interested in RERF because of my recent work related to radiation research, and because I had lived in Japan before. Though that opportunity did not open up at the time, partly because of the 2011 Tohoku earthquake



Reid D. Landes

and *tsunami*, RERF stayed on my mind. Another potential opportunity at RERF came open last year. I learned more about the objectives of RERF, and discussed the opportunity with my wife and department head. We all felt that it would be good to gain valuable experience in statistical methods used in large epidemiology studies and hopefully to contribute substantially to the work at RERF. My family and I decided to go for it. Fortunately, the opportunity was realized, and I was hired. Admittedly, my current plans are to strive to develop good collaborations during my two-year contract. When my contract concludes, I hope to introduce my RERF collaborators to U.S.-based researchers who can help in studies beneficial to both RERF specifically and radiation research in general.

On a personal level, I have been interested

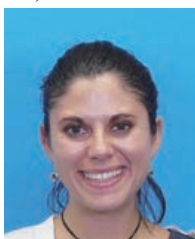
in Japan for quite some time. My best friend in kindergarten and first grade in elementary school was Japanese. In college, Japanese exchange students from Ibaraki Christian College came to my school, and we became friends. Then, after working as a high school math teacher in the U.S., I was blessed with an opportunity to work as an assistant English teacher in the Japanese Exchange Teaching Programme. I lived in what is now known as Minami-Soma, Fukushima. After returning to the U.S., I married my lovely wife, Angela. We have one daughter, Novelynn, and two sons, Andy and Jack. Away from work, I enjoy being with my family, worshipping my God, being with my church family, running, and (now) learning Japanese.

I look forward to making both professional and personal relationships with everyone.

Visiting Student Fellow

Caitlin M. Milder (Scheduled training period: October 24, 2013–October 23, 2014)

I am a visiting student fellow studying in the Epidemiology Department under the guidance of Dr. Eric Grant for one year. I am being funded through a David L. Boren Fellowship, a program for master's degree students to work and study in a field and country of importance to U.S. national security.



Caitlin M. Milder

I have spent most of my life in Arizona, and I graduated from the University of Arizona with two degrees—one in physiology and one in East Asian studies. A year prior to graduation, I spent six months at Waseda University in Tokyo studying Japanese in an intensive language program. Although I had planned to stay a year in Tokyo, my university requested that I return to the U.S. after the 2011 earthquake, *tsunami*, and Fukushima Dai-ichi nuclear disaster. My aim to combine my inter-

ests in Japanese and physiology in my professional life had already pushed me in the direction of international health and epidemiology; the Fukushima disaster fueled in me a desire to study the effects of radiation on human health. These combined interests drove me to seek out opportunities to study and work in the field of radiation epidemiology.

I am currently a master's student at the Johns Hopkins Bloomberg School of Public Health studying global-disease epidemiology and control in the Department of International Health. I spent my last year in Baltimore completing the coursework for my degree. The second half of my degree work is designed to take place in the field. I spent the last two months prior to joining RERF in Turkey working on statistical analyses of motivations for seatbelt use in Turkey and the Russian Federation as part of the Bloomberg Philanthropies' Road Safety in Ten Countries Project. I am delighted to have received the opportunity to study at RERF for my second and final internship. I would like to express my gratitude for the chance to grow, learn, and contribute to RERF's research.

Awards Received by RERF Scientist, General Staff

2013 Japanese Association of Cancer Registries Scientific Promotion Award

**Hiromi Sugiyama, Acting Chief
Tumor and Tissue Registry Office
Department of Epidemiology, Hiroshima**

At the 22nd meeting of the Japanese Association of Cancer Registries, held on June 14, 2013, I received the 2013 Scientific Promotion Award. This award, established in 2012, is presented to young researchers who contribute to research using population-based (well-defined population in a specific geographical region) cancer registry data.

The research theme for which I received the award was a review of how different methods of collecting population-based cancer registry data (record abstraction or notification, as indicated in the following paragraph) affected integrity (completeness), quality of data, and aggregation of data. The conclusion was that, although completeness of population-based cancer registry data could be assured by using only notified information, more detailed high-quality data could be collected using record abstraction by trained abstracters.

Hiroshima has cancer registries with different characteristics, such as the Hiroshima City Cancer Registry (information gathered on the basis of record abstraction), Hiroshima Prefectural Cancer Registry (notification received from hospitals), and Hiroshima Prefectural Tumor Registry (pathological registration), a situation that made it possible for me to conduct my review on this theme. Legislation concerning establishment of population-based cancer registries continues to make progress, and in the future hospitals will be legally obligated to make notification of cancers to the registries, ensuring that a certain level of data integrity will be achieved in all prefectures in Japan. To improve the quality of cancer registry data, however, continuous support, such as meetings to provide individuals in charge at medical institutions with explanations on how to fill out notification forms, will need to be provided.

The Japanese Association of Cancer Registries also presents the Distinguished Clerical Service Award to those who have achieved a certain level of technical skill in a central office overseeing regional cancer registries. Thus far, 10 Hiroshima

RERF employees have been commended. Ms. Saori Nakamura, who has rendered distinguished service for nine years, received the award this year. I am pleased that Ms. Nakamura and I, who both joined the RERF's registry office around the same time, were able to be awarded together.

At RERF, it is sometimes difficult and often challenging to manage regional cancer registry and tumor registry work as well as descriptive epidemiology research and, at the same time, conduct radiation epidemiology research. I have been able to continue my work thanks to the guidance I have received from other RERF researchers, individuals related to regional cancer registries in Hiroshima prefecture, and members of population-based cancer registry study groups. I would especially like to express my appreciation to my RERF colleagues who have lent their support to this cancer registry work. I ask for everyone's continued support and guidance.



Hiromi Sugiyama (left), Acting Chief, Tumor and Tissue Registry Office, and Saori Nakamura, the same office, with their awards

International Workshop: RERF Radiation Research in the Post-genomic Era

Yasunari Satoh, Research Scientist
Laboratory of Biochemical Genetics, Department of Genetics
Yasuharu Niwa, Associate Senior Scientist
Laboratory of Cell Biology, Department of Radiobiology/
Molecular Epidemiology

An international workshop was held on March 7 and 8, 2013, at the RERF Hiroshima Laboratory, under the theme “RERF Radiation Research in the Post-genomic Era.”

In recent years, research based on next-generation sequencing (NGS) has been flourishing in the fields of medical science and biology. NGS enables the collection of enormous amounts of experimental data never before possible. Although next-generation sequencers have not yet been introduced at RERF, it is essential for RERF to use NGS technology in its future research. The goal of the workshop was to discuss possible uses of NGS in determining radiation-induced mutation rates in human germ cells, and in studying radiation effects related to carcinogenesis, immune function, and epigenetics. Both of these research areas are important aspects of RERF’s mission, and nine researchers well known in these fields in Japan and abroad were invited to participate in the workshop to talk about recent progress in NGS-based research and future research possibilities at RERF using NGS.

Dr. Yoshiaki Kodama (Chief, RERF Department of Genetics) inaugurated the event by introducing the workshop’s aims and speakers. Dr. Jun-ichi Asakawa (Senior Scientist, RERF Department of Genetics) followed with a presentation titled “Brief notes on transgenerational effects of A-bomb radiation.”

The workshop consisted of five sessions. In the first, “*De novo* mutations in germ cells,” Dr. Yoichi Gondo (RIKEN; RERF Scientific Advisor) gave a lecture on “High-resolution detection of germline single nucleotide variations in the mouse by next-generation re-sequencing.” He reported that 1) NGS was used to detect base substitutions in the genome of F₁ mice produced by mating C57BL/6J male mice exposed to N-ethyl-N-nitrosourea (ENU), a chemical mutagen, with ENU-untreated DBA/2J female mice; 2) whole-exome sequencing was used to sequence approximately 50 Mb of the mouse genome that encompasses virtually all of the mouse coding regions; 3) about 100 ENU-induced base substitutions per F₁ mouse were detected; and 4) two of the strengths of this method were that a reliable mouse genome sequence—the sequence of the C57BL/6J mouse strain decoded in the Mouse

Genomes Project—was used as the reference sequence, and that the information about 600,000 known single nucleotide polymorphisms (SNPs) existing between the two strains of C57BL/6J and DBA/2J was used as the positive control.

The next speaker of the first session was Dr. Katie Campbell (University of Washington), who presented a talk titled “Estimating the human mutation rate using autozygosity in a founder population,” reporting on a study of large Hutterite families living in the United States. She reported that the aim of the study was to estimate the natural mutation rate in humans by examining almost identical regions of two chromosome strands of paternal and maternal origins that resulted from having a distant common ancestor on the paternal and maternal sides. The analysis showed a mutation rate of 1.21×10^{-8} mutations per base pair per generation, which increased 9-fold for bases within CpG dinucleotides (9.72×10^{-8}).

In the second session, “Detecting genetic variation and mutation using next-generation sequencer,” Dr. Ryan Mills (University of Michigan) gave a talk titled “Mapping structural variation by population-scale genome sequencing,” in which he presented the results of the 1,000 Genomes Project Consortium. He first reported on the results of the pilot phase of the project, which analyzed the whole genome sequences of 179 individuals across four ethnic groups: about 22,000 distinct deletions and 6,000 insertions and tandem duplications were detected. He also reported on the results of a subsequent phase of the project that analyzed an additional 1,092 individuals across 14 ethnic groups.

Dr. Mills’ talk was followed by a presentation from Dr. Akihiro Fujimoto (RIKEN) on “Comprehensive analysis of genetic variation by whole genome sequencing.” Dr. Fujimoto reported on the results of the first whole genome sequencing (WGS) of a Japanese individual, and of WGS of 27 hepatocellular carcinoma (HCC) cases. He reported 1) that about three million SNPs and 5,000 deletions were found in the WGS of the Japanese individual; 2) that a list of recurrently mutated genes in HCC was generated from the latter (27 HCC cases) WGS; 3) that multiple chromatin regulators were mutated in about half of the tumors

in the HCC WGS; and 4) that hepatitis B virus genome integration in the telomerase gene or the *MLL4* gene was frequently observed in HCC associated with hepatitis B.

In the third session, “Some data and ideas for future studies,” Dr. Yasunari Satoh (Research Scientist, RERF Department of Genetics) talked about a study, “Model experiments using irradiated human cultured cells,” being conducted in the Department of Genetics.

In the fourth session, “Applications of high-throughput sequencing to the immune system,” Dr. Harlan Robins (Fred Hutchinson Cancer Research Center) presented a talk on “Profiling the adaptive immune system with high-throughput sequencing.” He reported the results of detailed analyses using NGS of the immune system reconstructed by hematopoietic cell transplantation and the T-cell receptor repertoire in tumor-infiltrating lymphocytes. Dr. Ituro Inoue (National Institute of Genetics) then presented “Comprehensive analyses of *HLA* genomic region,” reporting on methods of human leukocyte antigen (*HLA*) genotyping with NGS.

In the fifth session, “RNA sequencing and epigenetics,” Dr. Yongli Xiao (U.S. National Institute of Allergy and Infectious Diseases) presented “High throughput RNA sequencing of an autopsy tissue sample from the 1918 influenza pandemic.” He reported that his team, using NGS, had sequenced the flu virus genome and transcripts extracted from formalin-fixed and paraffin-embedded (FFPE) lung tissue samples from two influenza pandemics, in 1918 and 2009. They succeeded in almost completely recovering the genome sequences of both flu viruses, 1918 and 2009, and identified an immune-related gene expressed in lung tissues as well as bacterial sequences associated with secondary bacterial infections. He also reported on the effectiveness of application of duplex specific nuclease (DSN) for minimizing ribosomal RNA effects.

Dr. Haruhiko Siomi (Keio University) followed with a talk titled “Small RNA-mediated transposon silencing,” reporting on PIWI, an element involved in the silencing of retrotransposons in the gonad. The presentation also described discovery of new functions of retrotransposons in genome evolution, and of such molecular complexes as small temporal RNAs. Dr.

Akira Watanabe (Kyoto University), addressing the topic “Genome and epigenome analysis of iPS cells for regenerative medicine,” talked about the use of NGS to construct genomic and epigenomic databases with the aim of producing clinically applicable induced pluripotent stem (iPS) cells. He reported that his team found a slight variation in the gene structure among iPS clones, and determined that a genomic and epigenetic match between iPS cells and the donor’s somatic cells is essential in the clinical application of iPS cells. The presentations in this session made everyone realize anew the importance of epigenetics in the post-genomic era.

The symposium concluded with a roundtable discussion chaired by Dr. Yoichiro Kusunoki (Chief, RERF Department of Radiobiology/Molecular Epidemiology). Symposium participants also toured the facilities and learned more about RERF’s research.

RERF benefited greatly from the symposium because RERF researchers were able to actively communicate with the visiting speakers and obtain their expert advice and cooperation concerning ongoing research at RERF as well as studies in the planning stages. These include model experiments using irradiated human cells in culture, studies of transgenerational radiation effects using mice, methods for detection of mutations and estimation of mutation rates, analysis of T-cell repertoires and epigenomics using archived lymphocytes that have been donated by A-bomb survivors on an ongoing basis, and RNA sequencing using autopsied tissue samples from A-bomb survivors.

We would like to express our appreciation to the Japanese Ministry of Health, Labour and Welfare, which funded the workshop; to the staff members of the Departments of Genetics and Radiobiology/Molecular Epidemiology; and to the many others who helped us organize the workshop.



Participants of the International Workshop: RERF Radiation Research in the Post-genomic Era

Third Meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors Held

Waka Ohishi, Acting Chief
Department of Clinical Studies, Hiroshima

The third meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors was held at the Hiroshima RERF Auditorium on April 25, 2013. At the meeting, progress in the longitudinal F₁ Clinical Study was reported. Dr. Nori Nakamura, Consultant, Department of Genetics, presented a talk on the topic “Past, present, and future—Heritable genetic effects of radiation on humans,” which suggested future directions of research on the genetic effects of radiation.

In the previous health effects study of the children of A-bomb survivors, a mail survey of 24,673 subjects and a clinical health study of 11,951 subjects were conducted between 2000 and 2006 to determine the relationship between parental radiation exposure and the prevalence of multifactorial diseases in children. The results of that study’s combined analysis of six multifactorial diseases (hypertension, hypercholesterolemia, diabetes, angina pectoris, myocardial infarction, and stroke) showed no evidence of increased risk related to parental radiation exposure. However, continuation of the study was recommended because in such prevalence studies there tends to be a bias related to decision-making among the participants concerning whether or not to undergo health examinations. Moreover, the average age of the subjects, about 49 years, was relatively low. In response to this recommendation, a research plan for the F₁ Clinical Study was approved, based on deliberations at the first meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors, held on July 7, 2010, which included experts from outside of RERF. Health examinations for the nearly 12,000 subjects were initiated on November 24 of the same year.

The meeting’s proceedings began with greetings and introduction of committee members by RERF Chairman Toshiteru Okubo, which was followed by greetings by Committee Chairman Tadao Shimao. Dr. Ohishi then reported on the progress made in the F₁ Clinical Study in the two years since its start. It was reported that the participation rate, including scheduled health examinations, increased from 69.2% in the first year to 76.0% for the two-year period overall, which was close to the targeted 80%. This increase was encouraging, in light of several measures that had been undertaken to improve the participation rate, including those recommended by members of the Scientific and Ethics

Committee at its second meeting, held on January 12, 2012, such as the effort to make contact by telephone with those whose addresses were unknown. It was then explained that further analysis of each of the individual multifactorial diseases using data obtained in the last prevalence study showed “no evidence suggesting increased risk for individual diseases related to paternal or maternal exposure to radiation.” The fact that these results were published in the *Journal of Radiological Protection* was also mentioned. Dr. Shimao praised the work, stating in the general discussion and in his summary that “the various efforts to improve the participation rate and the resulting high participation rate for the long-term continuous study showed that health examinations were being conducted properly in response to the needs of the subjects.”

After a brief recess, Dr. Nakamura presented his talk on the heritable genetic effects of radiation, reporting on genetic studies conducted at ABCC-RERF and a study of non-A-bomb childhood cancer survivors and their children. Finally, he explained in a readily understandable manner that the reason why heritable genetic effects of radiation were difficult to detect in humans was that a substantial number of variations are already accumulated as natural mutations in our DNA, as seen in recent genome analysis research. Under the direction of Dr. Shimao, vigorous questions were raised, after which the meeting concluded with remarks and words of appreciation by RERF Vice Chairman Roy E. Shore.

Based on the attempts to maintain and improve the participation rate in the F₁ Clinical Study, the number of participants is expected to increase in four years (one cycle) to more than 9,500, which is close to the original target of about 10,000. We would like to continue to encourage continuous



The third meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors held at the Hiroshima Laboratory

participation in the health examinations by distributing relevant information via letters and contacts by telephone, to ensure that the subjects understand the significance of our study as well as the fact that the health examinations at RERF could lead to early detection of diseases and improved overall health management.

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

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

Hiraku Takebe (Vice Chairman), Fellow, Kinki University Atomic Energy Research Institute

Hirotsugu Ueshima, Special Contract Professor, Lifestyle-Related Disease Prevention Center, Shiga University of Medical Science

Takashi Kawamoto, Professor, Graduate School of Education, The University of Tokyo

Shinsuke Kimura, Attorney, Kimura Shinsuke Law Office

Takashi Gojobori, Vice Director and Professor, National Institute of Genetics

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

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

Kazuo Tajima, Director, Aichi Cancer Center Research Institute

Masao Tomonaga, Director, Japanese Red Cross Nagasaki Atomic Bomb Hospital

Taisei Nomura, Professor Emeritus, Osaka University

Norihiko Hayakawa, Professor Emeritus, Hiroshima University

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

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

RERF Participants

Toshiteru Okubo, Chairman

Roy E. Shore, Vice Chairman

Takanobu Teramoto, Executive Director

Kazunori Kodama, Chief Scientist

Eiji Akimoto, Chief of Secretariat

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

Fourth Epidemiological Training Workshop for Biologists

Ritsu Sakata, Associate Senior Scientist Department of Epidemiology, Hiroshima

The fourth Epidemiological Training Workshop for Biologists, hosted by the Council of Radiation Effects Research Organizations, was conducted on August 26–27, 2013, at the RERF Auditorium in Hiroshima. This workshop was initiated in 2010 at the suggestion of Dr. Nori Nakamura, then RERF Chief Scientist, to promote mutual exchange between biologists and epidemiologists. Dr. Nakamura had organized the workshops since they began, but starting in 2013, when Dr. Nakamura became Consultant to the Department of Genetics, the Department of Epidemiology assumed responsibility for the event. Initially, enrollment for this year's workshop lagged, partly because other radiation-related meetings were taking place around the same time, and we thus prepared for a small turnout. However, the number of applicants increased after mid-July, and eventually 32 participants, including 11 from RERF, joined

the workshop. (The Council of Radiation Effects Research Organizations, established to develop understanding and enhanced collaboration among radiation research organizations, consists of the Institute for Environmental Sciences, Kyoto University, Nagasaki University, Hirosaki University, Hiroshima University, Fukushima Medical University, National Institute of Radiological Sciences, and RERF.)

On the morning of the first day, participants listened to the lectures "Radiation biology for non-biologists" by Dr. Nakamura; "Epidemiology for non-epidemiologists" by Dr. Sakata, Associate Senior Scientist, Department of Epidemiology; and "Descriptions of Life Span Study Report 14" by Dr. Kotaro Ozasa, Chief, Department of Epidemiology. Afternoon sessions included "Genetic effects in A-bomb survivors" by Dr. Yoshiaki Kodama, Chief, Department of Genetics; "Com-

mentary on a paper: Risk of CT scans in childhood” by Dr. Atsuko Sadakane, Associate Senior Scientist, Department of Epidemiology; “Risk in the offspring of A-bomb survivors” by Dr. Eric J. Grant, Assistant Chief, Department of Epidemiology; and “Risk from *in utero* exposure to radiation” by Dr. Hiromi Sugiyama, Acting Chief, Tumor and Tissue Registry Office, Department of Epidemiology.

In the evening of that first day, a party took place at a venue outside of RERF. In addition to most of the workshop participants, RERF Chairman Toshiteru Okubo, Vice Chairman Roy E. Shore, and Chief Scientist Kazunori Kodama attended the gathering. The participants engaged in conversation about their specializations, exchanged opinions, and enhanced mutual understanding. At the event, the younger participants expressed the need for more opportunities to speak, a desire that came to fruition on the second day of the workshop, when younger researchers were more active, presenting a number of questions and comments.

The second day’s lectures included “Cardiovascular disease risk among A-bomb survivors” by Dr. Ikuno Takahashi, Research Scientist, Departments of Epidemiology and Clinical Studies; “What

age at exposure means” by Dr. Nakamura; and “Trends in radiation effects studies outside Japan” by Dr. Otsura Niwa, Professor Emeritus, Kyoto University. A discussion about the future of the workshop followed, during which numerous views were presented. One participant proposed that the current workshop, which is designed for beginners, and a study meeting intended for research discussion be held in alternate years. Another idea expressed was that the workshop should provide an opportunity to discuss future directions in radiation effects research. Another participant requested that the topic of risk communication be included in the workshop. Other participants, on the other hand, requested continuation of the current workshop’s focus on basics. Reasons offered for this argument were that not all researchers engaged in radiation effects research have attended this workshop, and that the workshop has been useful in recalling the epidemiological mindset, which tends to be forgotten in the course of day-to-day work. Because this was the fourth training workshop, and because the number of participants was down this year, it seemed necessary to discuss the program’s future; we are truly grateful for the many productive comments we received from the participants.



Participants of the fourth Epidemiological Training Workshop for Biologists

The Incidence of Leukemia, Lymphoma and Multiple Myeloma among Atomic Bomb Survivors: 1950–2001*

Dale L. Preston¹ and Harry M. Cullings²

¹HiroSoft International Corporation, USA (Consultant, Department of Statistics, RERF)

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*This article is based on the following publication:

Hsu WL, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, Kimura A, Kamada N, Dohy H, Tomonaga M, Iwanaga M, Miyazaki Y, Cullings HM, Suyama A, Ozasa K, Shore RE, Mabuchi K. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. *Radiat Res* 2013; 179(3):361–82 (doi: 10.1667/RR2892.1)

Study Findings

This report represents a 14-year update of findings on radiation risks for cancer-like diseases of the blood and lymphatic systems and provides unique data regarding several questions:

What are the cumulative risks of these cancers since the atomic bombings? The data show a total excess of 94 leukemia cases associated with radiation exposure among the 113,011 Life Span Study (LSS) members. There was no excess of Hodgkin lymphoma (HL), and a marginal excess of non-Hodgkin lymphoma (NHL) among males but none among females. There was no clear excess of multiple myeloma (MM).

How large is the risk at low doses? There was a dose response with upward curvature for the radiation-related group of leukemia sub-types, which implies there is less risk per mGy unit of dose at low dose levels than at higher ones. In addition, risks varied markedly by time since exposure, age at exposure, and leukemia sub-type.

Has the excess leukemia risk disappeared by this many years after the bombings? Although the excess risks generally declined with increasing age or time since exposure, there was evidence that the radiation-associated excess risks, especially for acute myeloid leukemia (AML), have persisted throughout the follow-up period, though the excess risks are low by 55 years after the bombings.

Explanation

Leukemia and other cancer-like diseases of the blood and blood-forming organs are typically studied together and considered to be different in various aspects from other, i.e., “solid” cancers. The diseases grouped here with leukemia include cancers of the lymphoid system (lymphomas) and

MM, a cancer of white blood cells called plasma cells.

After exposure to ionizing radiation such as that from the A-bombs, the risk of leukemia increases sooner than that of the solid cancers, and leukemia was the first and most striking late effect of radiation exposure seen among the Hiroshima and Nagasaki atomic bomb survivors. Leukemia also has a very high relative risk per unit radiation dose, compared to most solid cancers.

Leukemia has a number of sub-types, most of which are considered to be associated with radiation exposure but some not. Even among the radiation-associated sub-types, in addition to analyzing them as a group, there is an interest in analyzing their radiation risks separately to see how they differ. Lymphoma is also not a single disease, having the two major classifications HL and NHL.

Because a number of years had passed since the last comprehensive RERF study of the incidence of leukemia, lymphoma, and multiple myeloma, there was a need for an update. This was a considerable undertaking due to concerns about changes that had occurred in the classification of these diseases and their sub-types. RERF researchers, in collaboration with external researchers from Hiroshima and Nagasaki, undertook a new analysis, which includes 14 years of additional follow-up since the last report, along with an expanded selection of risk models.

1. Objective of the study

The objective of this study was to provide comprehensive, updated risk estimates for the incidences of leukemia, lymphoma, and multiple myeloma (MM) in relation to A-bomb radiation dose.

2. Study methods

Incident cases were ascertained and assembled from the Leukemia Registry and the Hiroshima and Nagasaki Tumor Registries using a series of rules to give precedence to the better information when there were discrepancies, providing incidence data on 113,011 LSS cohort members with 3.6 million person-years of follow-up from late in

1950 through the end of 2001. Risk estimates were made using Poisson regression on highly stratified tables of these data to characterize the shape of the radiation dose-response relationship and, to the extent the data allowed, to investigate variation in the excess risks with gender, attained age, exposure age, and time since exposure. Both excess absolute rate (EAR) and excess relative risk (ERR)

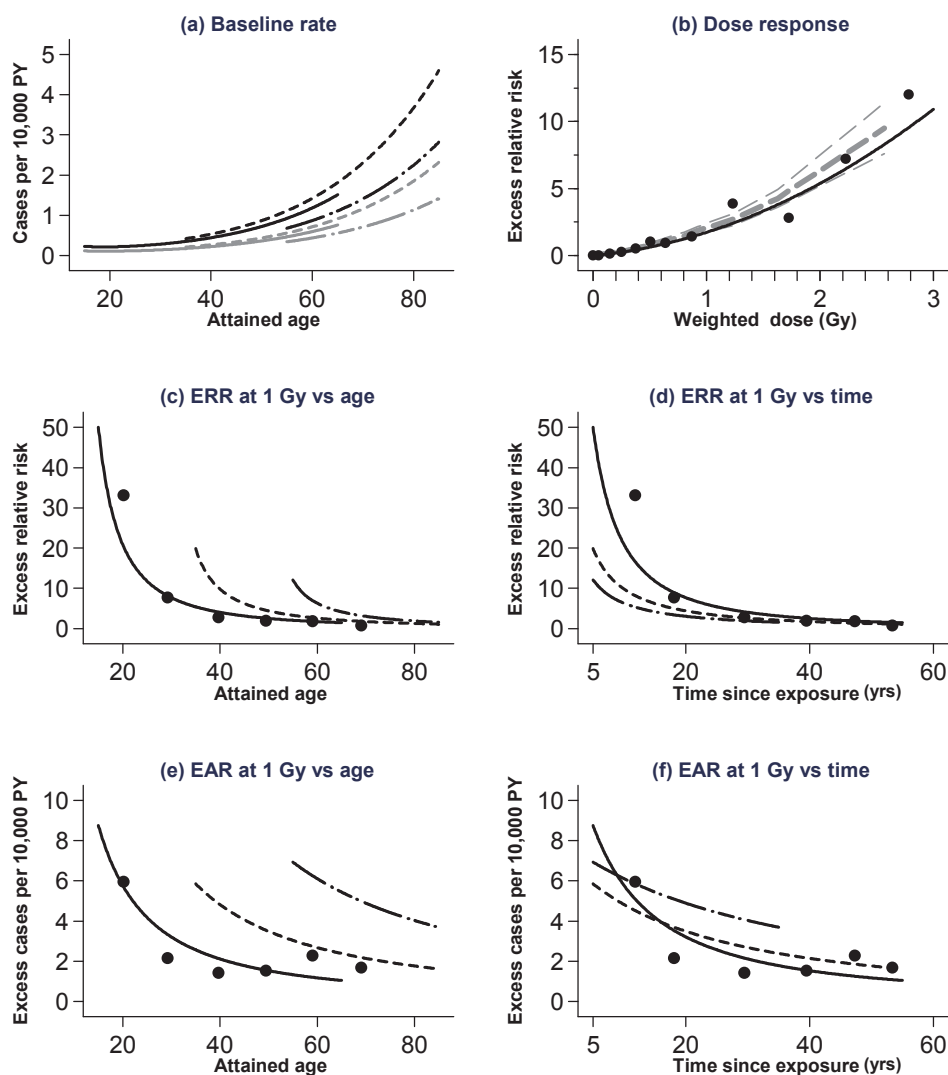


Figure. Summaries of the risk of leukemia other than CLL or adult T-cell leukemia (ATL) in the LSS. Plot (Panel a) shows age-specific baseline (zero dose) rates in Hiroshima for men (black lines) and women (gray lines) for LSS cohort members born in 1895 (dash-dot line; age at exposure 50), 1915 (dash line; age at exposure 30), and 1935 (solid line; age at exposure 10). Panel b: illustrates the radiation dose response based on the ERR model with risks standardized to attained age 70 for a person exposed at age 30 (born in 1915). The solid-black line illustrates the fitted linear-quadratic dose response. The points are based on a nonparametric dose-response model, while the middle-dashed-gray line is a smoothed version of the dose category-specific estimates from the nonparametric fit. The upper- and lower-dashed-gray lines are plus and minus one standard error from the smoothed fit. Panels c and d: illustrate the temporal pattern and age-at-exposure effects for our preferred ERR model (ages at exposure indicated by lines are same as in Panel a). The fitted ERR did not depend on either gender or city. Panels e and f: present the temporal pattern and age-at-exposure effects for Hiroshima males based on the preferred EAR model (ages at exposure indicated by lines are same as in Panel a). The points in Panels c-f are nonparametric estimates for exposure at age 10.

models were considered. (The ERR is based on the assumption that radiation-related risk is proportional to the baseline [zero dose] risk, which typically may vary by age, sex, and other factors, while the EAR assumes that the radiation-related risk does not depend on the level of the baseline risk.)

3. Results

- (1) A total of 1,215 hematological malignancies were identified among LSS cohort members, 944 of which were eligible for inclusion in the analyses between 1950 and the end of 2001. Almost 40% of the eligible cases were diagnosed after the end of the follow-up (1987) used in the last comprehensive analyses of the LSS data. About 40% of the cases were leukemias, another 40% were identified as NHL, and almost 15% were MM. HL was uncommon. Almost half of the leukemia cases were classified as AML, 20% were chronic myeloid leukemia (CML), and about 12% were acute lymphoblastic leukemia (ALL). As with other populations in Japan, the incidence of chronic lymphocytic leukemia (CLL) was remarkably low.
- (2) For the “radiation-related” group of leukemia sub-types consisting of AML, ALL, and CML, allowing for attained-age and time-since-exposure effects in the model, a concave upward linear-quadratic (LQ) model that contains a term for dose and a term for dose-squared described the data significantly better than either a linear dose-response or pure quadratic

dose-response model (Figure). The estimated linear dose effect in the LQ ERR model at attained age 70 after exposure at age 30 was 0.79 (i.e., a 79% excess) at 1 Gy and the estimated curvature was 1.2, which means that the risk coefficient for the square of dose was 1.2 times the coefficient for the linear dose effect. For example, the total ERR at 1 Gy was $0.79 \times (1 + 1.2 \times 1^2) = 0.79 \times 2.2 = 1.74$, whereas the ERR at 0.01 Gy would be $0.79 \times (0.01 + 1.2 \times 0.01^2) = 0.79 \times 0.01012$, which is very close to 0.79/100—the dose-squared term contributes almost nothing. Thus the estimated risk at lower doses is substantially less than it would be for a purely linear dose response with the same total ERR of 1.74 at 1 Gy. It was estimated that about 94 of the 312 cases of AML/ALL/CML leukemia used in these analyses were associated with the radiation exposure.

- a. For AML analyzed separately (176 cases), a pure-quadratic model with an estimated ERR at 1 Gy of 1.11 (standardized to age 70 after exposure at age 30) described the data as well as a linear-quadratic model.
 - b. For NHL (402 of 437 lymphoma cases), while there was some evidence of a statistically significant radiation effect in men, there was no indication of a radiation effect in women.
- (3) There was no evidence of radiation-associated excess risk for HL or MM.

Radiation-dose Response of *Glycophorin A* Somatic Mutation in Erythrocytes Associated with Gene Polymorphisms of *p53 Binding Protein 1**

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*This article is based on the following publication:

Yoshida K, Kusunoki Y, Cologne JB, Kyoizumi S, Maki M, Nakachi K, Hayashi T. Radiation-dose response of *glycophorin A* somatic mutation in erythrocytes associated with gene polymorphisms of *p53 binding protein 1*. *Mutat Res* 2013; 755(1):49–54 (doi: 10.1016/j.mrgentox.2013.05.003)

Study Findings

Previous studies revealed that the fraction of erythrocytes with somatic mutations at the *glycophorin A* (*GPA*) gene locus increased with radiation dose in atomic-bomb survivors. It was found in the present study that the manner in which *GPA* mutations increased following radiation exposure (radiation-dose effects) differed by individual differences in genetic background, i.e., DNA sequences (gene polymorphisms). It also was suggested that *p53* binding protein 1 (*53BP1*) plays a significant role in DNA double-strand break repair in hematopoietic stem cells following radiation exposure.

(Note) Use of letters in italics, such as in *GPA* and *53BP1*, indicates genes, whereas ordinary typeface, such

as *GPA* and *53BP1*, is used to designate proteins generated by those genes. *GPA* gene mutations are usually confirmed by the observation of protein alterations.

Explanation

The fraction of erythrocytes with mutations at the *GPA* gene locus is considered to be one of the indices of somatic mutations induced by ionizing radiation for estimating the degree of related genome damage and cancer risk. Previous studies of A-bomb survivors revealed that erythrocyte *GPA* mutations increased with radiation dose, but it also was reported that there was significant individual difference in *GPA* mutation rates even after exposure to around the same radiation dose. The reason for such individual difference in *GPA* mutation rates was unclear, and the differences could not be

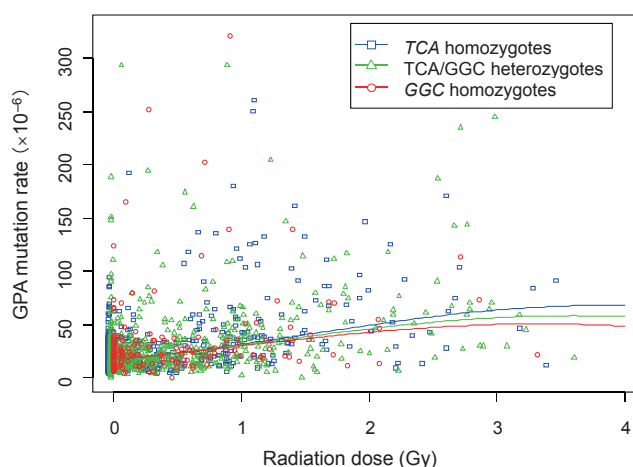


Figure. Relationship among *GPA* mutations, radiation dose, and *53BP1* gene polymorphisms. Increase in *GPA* mutations varies by individual differences in DNA sequence of the *53BP1* gene. (Individuals with *TCA* homozygotes, *TCA/GGC* heterozygotes, and *GGC* homozygotes are shown in blue, green, and red, respectively.)

explained by differences in age at exposure, sex, city, or frequency of smoking.

In the present study, we examined whether individual differences in DNA sequences (gene polymorphisms) contributed to individual differences in GPA mutation rates related to radiation exposure. In particular, because it was suspected that the difference in ability to repair DNA double-strand breaks that are caused by radiation exposure may be related to individual differences in GPA mutation rates, we focused on gene polymorphisms of the *53BP1* gene, which is related to DNA double-strand break repair. As a result, radiation-dose effects on GPA mutation rates were found to vary slightly by *53BP1* gene polymorphism (Figure).

Although erythrocytes have a short life span of around 120 days, an increase in the number of

erythrocyte GPA mutations with radiation dose is still observed even now, more than 60 years after A-bomb radiation exposure. It can therefore be considered that mutations have been recorded in the *GPA* genes of longer-lived hematopoietic stem cells, which can differentiate into erythrocytes. In other words, it is assumed that many of the erythrocyte GPA mutations observed in A-bomb survivors reflect GPA mutations in hematopoietic stem cells. For this reason, and because of the relationship between erythrocyte GPA mutations and *53BP1* gene polymorphisms observed in the present study, it is suggested that a group of proteins, including 53BP1, plays an important role in DNA double-strand break repair in hematopoietic stem cells and somatic mutations following radiation exposure.

Alterations of Body Mass Index and Body Composition in Atomic Bomb Survivors*

Yoshimi Tatsukawa

Department of Clinical Studies (Hiroshima), RERF

*This article is based on the following publication:

Tatsukawa Y, Misumi M, Yamada M, Masunari N, Oyama H, Nakanishi S, Fukunaga M, Fujiwara S. Alterations of body mass index and body composition in atomic bomb survivors. *Int J Obes* 2013; 37(8):1123–8 (doi: 10.1038/ijo.2012.193)

Study Findings

Both body mass index (BMI) and muscle mass index tended to decrease with increased radiation dose in both male and female A-bomb survivors. Abdominal obesity index tended to increase among females who were younger than 15 years of age at the time of bombing (ATB).

Explanation

We examined the relationship of radiation exposure to BMI and to body composition measured by systemic dual-energy X-ray absorptiometry (DXA) among subjects of the Adult Health Study (AHS), a long-term follow up of the health of A-bomb survivors based on biennial health examinations.

1. Study purpose

No study has been conducted on whether A-bomb radiation affected obesity or body composition such as muscle and fat. This paper resulted

from a study on whether radiation exposure is related to alterations of BMI and of body composition measured by DXA, taking age ATB into consideration.

2. Study methods

Relationship between radiation exposure and BMI was examined for 2,686 A-bomb survivors (834 males and 1,852 females) aged 48–89 (0–40 years ATB) who had participated in the AHS during the period 1994–1996. Further, the relationship between radiation exposure and body composition was examined for 1,729 of those survivors (550 males and 1,179 females) for whom body composition had been assessed by DXA.

In reviewing body composition, we used 1) fat-free mass of extremities (both arms and both legs; weight minus weight of bone and fat)/height squared, as an index of muscle mass, and 2) ratio of trunk fat to extremity fat, as an index of abdominal

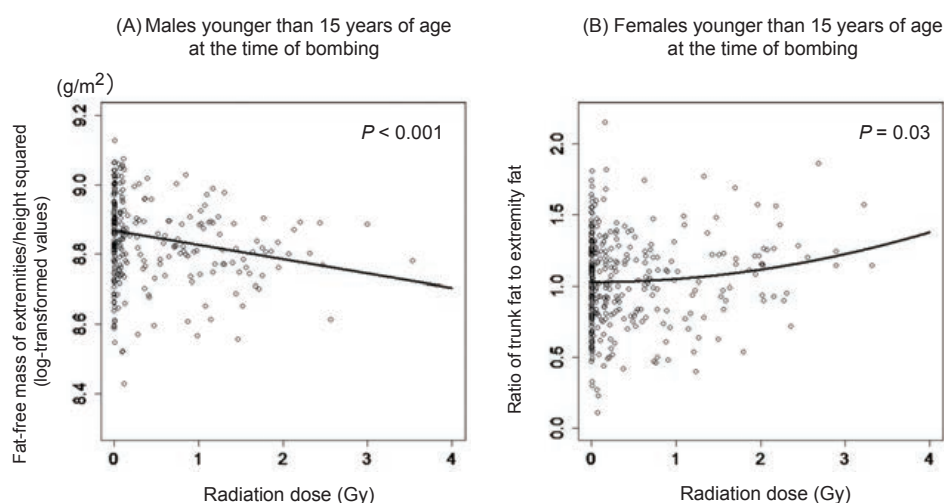


Figure. Relationship between body composition and radiation dose in atomic-bomb survivors. Index of muscle mass (fat-free mass of extremities/height squared) among males who were younger than age 15 ATB (Panel A), and index of abdominal obesity (ratio of trunk fat to extremity fat) among females who were younger than age 15 ATB (Panel B)

obesity. In statistical analysis, age at examination, age ATB (ages <15, ≥15), serum creatinine level, smoking and alcohol consumption status, presence of diabetes, history of ischemic heart disease and malignant tumor, and menopausal status for females were taken into consideration.

3. Study results

(1) Effects of radiation on BMI

BMI tended to decrease with increased radiation dose in both males and females. Analysis by age ATB showed a significant relationship between increased radiation dose and decreased BMI among males who were younger than age 15 ATB.

(2) Effects of radiation on body composition

Muscle mass index decreased with increased

radiation dose. As in the case of BMI, examination by age ATB showed that the muscle mass index tended to decrease with increased radiation dose among males who were younger than age 15 ATB. Among females who were younger than age 15 ATB, the abdominal obesity index tended to increase quadratically with radiation dose (Figure).

In this investigation of A-bomb survivors around 50 years after A-bomb radiation exposure, decreased BMI and altered body composition with increased radiation dose were suggested. Further investigation is underway on how such body composition alterations are involved in the health status of A-bomb survivors.

A Retrospective of My Work at the Radiation Effects Research Foundation

Masazumi Akahoshi, Former Chief
Department of Clinical Studies, Nagasaki

After being dispatched to RERF as part of a rotation at the Third Department of Internal Medicine, Nagasaki University, in April 1988, I served at RERF for 25 years, until the end of March 2013.

I remember that when Dr. Stuart Finch, then Chief of Research, asked me what I hoped to do at RERF, I stated that I wanted to conduct research on circulatory diseases, and that even though I was not interested in the health effects of radiation, I would do my best to cooperate in research. Because he did not fire me then, I thought my conditions had been accepted. In the fall of the same year, Professor Kondo of the Department of Neurology, Hokkaido University, requested that the RERF Nagasaki Laboratory participate in a research team on dementia, and it was decided, due to a recommendation from Clinical Studies Department Chief Kyoko Toyama, that I would participate. I never dreamed that this event would affect my future to the extent that it did.

When I was preparing materials for the second meeting of the research team in November or December 1989, I was warned not to give away so many of the data to the team's research because RERF and U.S. researchers were planning to start a dementia study shortly thereafter. I was furious but pledged to myself that I would not resign from RERF until I created an environment in which the Nagasaki Laboratory could take the lead on its own research. That marked the beginning of my research career.

In the early 1990s, based on suggestions from Drs. Midori Soda and Yasuko Amasaki, I started collecting RERF data related to the themes menopause and cholesterol, the relationship between body weight and blood pressure, and fatty liver and ischemic heart disease. Around that time, Drs. Hiroaki Nonaka and Masako Tsuruta, who were well versed in computer programs, Ms. Kaoru Yoshida, who was interested in computers, and Mr. Shinichiro Ichimaru, who was strong in mathematics, were assigned to our department. My epidemiological research advanced gradually with their help and also thanks to a suggestion by Dr. Dale L. Preston of the Department of Statistics that I consult with Dr. Eiji Nakashima concerning all matters related to statistical analyses at the Nagasaki Department of Clinical Studies. In the late 1990s,

I started to publish papers on Nagasaki RERF's own research in scientific journals (*Circulation* and *American Journal of Epidemiology* [1996], *Atherosclerosis* and *Hypertension Research* [2001], *International Journal of Obesity and Related Metabolic Disorders* [2002], and *Hypertension Research* [2006]).

At a workshop held at the Hiroshima Laboratory at the beginning of this new century, I presented my research showing that fatty liver (metabolic syndrome) was somehow involved in the developmental mechanisms of myocardial infarction among A-bomb survivors. Workshop participants severely criticized my presentation, indicating their doubts that fatty liver developed due to radiation exposure. This rekindled my fighting spirit, and I ultimately succeeded in publishing a paper on the relationship between fatty liver and radiation exposure (*Hypertension Research* [2003]), breaking my original promise with Dr. Finch.

In 2000, doctors dispatched from the First Department of Internal Medicine, Nagasaki University, started to serve at RERF for extended periods, and as the department chief, I became deeply involved in their studies on radiation health effects. I was engaged in the research from the planning stage to analysis, conducting group discussions with Dr. Ayumi Hida (Sjögren syndrome; *Nutrition and Cancer* [2005], *Annals of the Rheumatic*



Masazumi Akahoshi in his office at RERF

Disorders [2008, 2010], *Experimental and Clinical Endocrinology and Diabetes* [2012]), Drs. Misa Imaizumi, Tan Tominaga, and Toshiro Usa (the thyroid; *Journal of Clinical Endocrinology and Metabolism* [2004, 2005], *JAMA* [2006], *Journal of Clinical Endocrinology and Metabolism* [2008], *Thyroid* [2011]), Dr. Kiyoto Ashizawa (the thyroid; *Clinical Endocrinology* [2010]), and Dr. Nobuko Sera (chronic kidney disease; *Radiation Research* [2012]). This experience of uncovering the health effects of A-bomb exposure with other researchers was valuable for me.

Around the same time, Drs. Kiyotaka Matsuo, Takeshi Baba, Manabu Moriya, Akira Tsuneto, Daisuke Haruta, and Saburo Kusumoto joined RERF from the Third Department of Internal Med-

icine, Nagasaki University, and conducted interesting research for the purpose of obtaining their doctoral degrees. Especially in the field of cardiac arrhythmia, I was fortunate to engage in epidemiological research of lethal arrhythmia based on new concepts.

Starting now, I would like to return to the early days of my career and contribute to community medical care at a nursing complex designed for medical care, centering on a long-term care concept. This facility includes Japan's first large-scale long-term nursing home for the elderly, as well as a special care-unit nursing home, which is one of just a dozen such nursing homes in Japan.

In conclusion, my 25 years at RERF were full of interesting human relationships.

Report on the 19th Health Examination Project for A-bomb Survivors in North America

**Yoshimi Tatsukawa, Associate Senior Scientist
Department of Clinical Studies, Hiroshima**

The health examination project for A-bomb survivors resident in North America was initiated under the sponsorship of the then Ministry of Health and Welfare in 1977 as a collaborative mission between the Hiroshima Prefectural Medical Association (HPMA) and RERF. The activity, folded in 2007 into a project initiated by the present-day Ministry of Health, Labour and Welfare (MHLW) to support A-bomb survivors living overseas, has been entrusted by MHLW to the Hiroshima prefectural government, and then by the prefecture to the HPMA. A medical team is dispatched to four cities in the U.S. (Los Angeles, Honolulu, San Francisco, and Seattle) every two years, and this was the 19th such project. I visited San Francisco and Seattle during the last (18th) mission and this year stayed in the Los Angeles area (city of Torrance) and Hawaii (Honolulu) for 13 days, from June 26 to July 8, to engage in health examinations for A-bomb survivors. I am grateful to the research scientists and other staff members at the Department of Clinical Studies who supported health examination activities at RERF during my absence.

The Los Angeles and Hawaii medical team that I took part in this time was led by Dr. Jitsuro Yanagida (Permanent Director, HPMA) and consisted of a total of 10 members, including five physicians, a gynecologist who participated in

the health examinations only in Hawaii, and four administrative staff members dispatched by the Hiroshima and Nagasaki city governments and the HPMA. An employee from the Hiroshima prefectural government later joined the team in Hawaii as an investigator. The male physicians must have felt uncomfortable, as four out of the six physicians and all the administrative staff members were female. The San Francisco and Seattle medical team conducted health examinations over 15 days for A-bomb survivors resident in North America, from July 17 to 31.

A major system change was instituted for this 19th project in Los Angeles and Hawaii. Previously, we conducted blood and other tests during our visits to North America. This time, however, A-bomb survivors underwent health exams at local medical facilities in advance, and five physicians of the team explained the results and provided healthcare advice to the examinees. In addition, lung and stomach cancer screening was introduced. Although there was some confusion due to the change, we were able to complete the project successfully with instruction from Dr. Yanagida and cooperation from the staff members. I was very relieved to hear an A-bomb survivor in Los Angeles indicate that he was grateful to be able to listen to our explanation of the exam results in Japanese, rather than simply to receive exam results as was

done in the past. I realized how different medical care is in Japan and the U.S. when I participated in the previous tour, but it was educational for me this time to be able to read detailed U.S. chest and stomach X-ray reports and see just how differently they are handled compared with Japanese hospitals.

The number of A-bomb survivors undergoing health examinations is on the decline due to aging, and those who have been supporting this North America project for so long are also aging. We will need to review how to conduct health examinations in North America in the future based on our experi-

ence from this visit. I hope the health examination project that has been conducted over these years since its inception will continue to be a bridge of medical support for A-bomb survivors living in North America.

In conclusion, for the support and cooperation they have provided to the health examination project, I would like to express my sincere appreciation to the American Society of Hiroshima-Nagasaki A-bomb Survivors, local medical associations and physicians, Providence Little Company of Mary Medical Center Torrance (Los Angeles), Kuakini Medical Center (Hawaii), and all of our volunteers.



At the venue of A-bomb survivors' health examination program in Los Angeles. Yoshimi Tatsukawa, author, is fifth from the right at rear.

Results of Review of Basic Information Used in Individual Dose Estimates and Recalculation of Radiation Risks

Toshiteru Okubo, Chairman

With publication of the dosimetry system DS02 (in 2003), a method for estimation of individual radiation doses was completed, but work involving reexamination of exposure locations remained. We recently completed that work by achieving 1) consistency in use of number of digits for coordinate information of exposure locations, 2) adjustment of distortions in U.S. Army maps, and 3) re-identification of exposure locations using a geographic information system (GIS).

History of work

Nov. 2007 Start of review of original survey records for the Life Span Study (LSS) cohort

Review of data entered on the basis of original Master Sample Questionnaire (MSQ) forms (confirmation of exposure locations/coordinates); entry of items for which no data had been entered in the past (date and location of entry into the city, “black rain” exposure/non-exposure); this process led to discovery of inconsistency in number of digits used for the entered data.

Apr. 2009 Establishment of Dosimetry Committee

May 2010 Completion of orthorectification* of composite aerial photographs

Dec. 2010 Completion of triangular interpolation calculation formula for correction of map distortions

Feb. 2011 Initiation of work to reconfirm exposure locations using aerial photographs and neighborhood drawings

Mar. 2012 Completion of abovementioned work

*Orthorectification is a process whereby an aerial photograph is geometrically corrected to eliminate distortions from topographic relief, lens distortion, and camera tilt.

Report on results of work

1) Correction of inconsistency in data entry of exposure location coordinates—Effects of restoring truncated digits used for the entered data

Starting in 2007, coordinate and other data regarding exposure locations were reexamined

on the basis of the MSQ records of LSS subjects, and data that had not previously been input were entered. This data work was completed in 2010. It was found that, for a majority of LSS subjects without shielding survey records, digits for tens of yards (up to but not including 100 yards, or 91.4 m) in the map coordinates had been truncated in the original data (Table). This resulted in a difference between actual distances from the hypocenter and the entered distances of up to 127 yards. A difference of 100 m at a distance of 2 km from the hypocenter results in a difference of 30 mGy in air kerma dose in Hiroshima or 55 mGy in Nagasaki.

All of the previously truncated data were then restored. Overall, distance from the hypocenter became slightly closer in Hiroshima but farther in Nagasaki.

Table. Digit-restoration cases compared with cohort subject numbers

	Entire LSS cohort members	A-bomb survivors in the cohort	Number of truncated-digit cases (%)
Hiroshima	82,214	61,984	33,464 (54.0)
Nagasaki	38,107	31,757	24,350 (76.7)
Total	120,321	93,741	57,814 (61.7)

2) Correction of map distortions and elongation—Systematic revision for non-shielding-survey subjects

Based on use of aerial photographs of Hiroshima and Nagasaki prior to the atomic bombings, simple orthorectified aerial photographs with coordinate information were created of both cities. Common points on these simple orthorectified photographs and the army maps (about 100 common points for each city) were determined for comparison purposes, and the images of the army maps were mathematically stretched within triangles connecting these points to correct any distortions. In addition, the army map coordinates used until that point in time for exposure location coordinates were converted to new plane rectangular coordinates.

Subjects of this systematic correction numbered 70,995 people for whom no shielding survey

records were available. Of this total, 12,465 people were located within 2,000 m of the hypocenters. The distortions in Hiroshima were larger, and with the correction process, there was an area oriented from northwest to southeast in which distances from the hypocenter became farther by around 10–50 m, and an area at a fairly significant distance to the north in which distances became closer by more than 50 m (refer to map of Hiroshima in Figure 1).

3) Methods and results of precise determination of exposure locations

For 22,746 cases with shielding survey records, GIS software was used to superimpose neighborhood drawings on the aforementioned simple orthorectified aerial photographs, with precise exposure locations being re-determined. At the same time, recalculation of distance from the hypocenter based on the plane rectangular coordinates of the obtained A-bomb exposure locations was carried out. As a result, the differences in distance from the hypocenters showed bilaterally symmet-

ric distribution, with changes due to the revisions being in the range of ± 50 m in both cities (Figure 2). Estimates showed that only a very small systematic error was involved: the center of distribution shifted slightly away from the hypocenter in each of the cities, with the average shift in distance being 5 m in Hiroshima and 4 m in Nagasaki.

4) Effects of corrections described in 1)–3) above on radiation doses and cancer risks

The plots comparing new and old individual doses (Figure 3) show doses in both cities to be distributed more or less evenly about a line at a 45-degree angle that represents no change, with the average doses remaining unchanged. With regard to the distribution of differences between the new and old doses, the differences were slightly larger in Nagasaki, and the distribution of the new doses was systematically lower especially at 100 mGy or less. Only the all-solid-cancer risk calculations have been completed, and the excess relative risk changed only slightly, from 0.427 to 0.450, with no significant effects on confidence intervals.

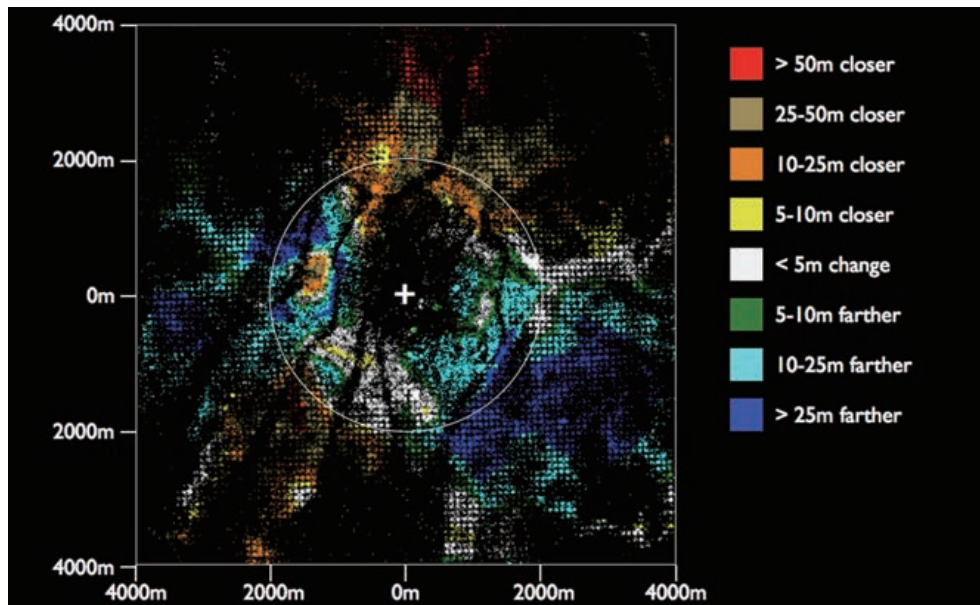


Figure 1. Hiroshima: Change of ground distance due to “rubber sheeting”

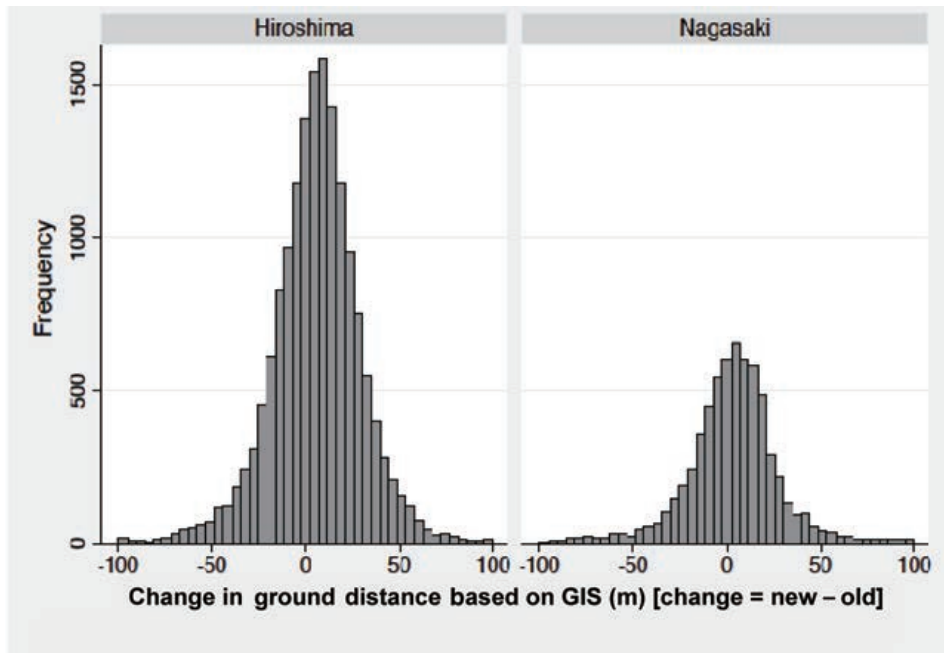


Figure 2. Ground distance change

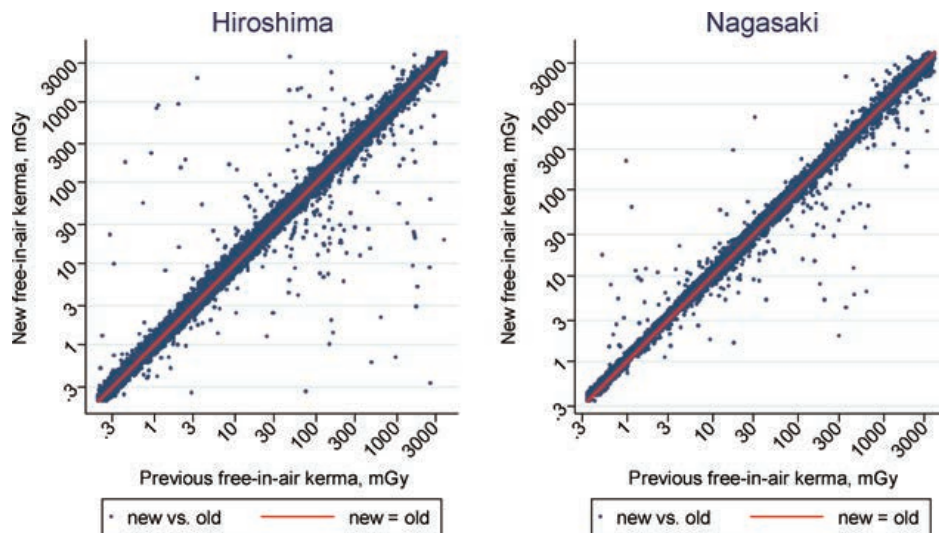


Figure 3. Changes in dose estimates

Research Protocols Approved in May–October 2013

RP 1-13 Analyses of Molecular Characteristics of Lung Cancer among Atomic-bomb Survivors

Taga M, Hamatani K, Ito R, Niwa Y, Grant EJ, Ozasa K, Katayama H, Misumi M, Sui H, Harris CC, Yasui W, Kusunoki Y

Background: Excess relative risk of lung cancer among atomic-bomb (A-bomb) survivors remains high even now, more than 60 years after the bombings, indicating a prolonged radiation effect on development of lung cancer. One approach to seek at the molecular level how radiation exposure affected development of lung cancer was initiated in a pilot study (RP B37-04). Preliminary results suggest the possibility that frequencies of certain gene mutations (e.g., the *TP53* tumor suppressor gene) and methylation levels (e.g., the retrotransposon *L1NE1*) may be associated with radiation exposure. However, molecular alterations observed in the pilot study mainly lacked statistical significance in terms of radiation dose, and smoking effects were excluded from the statistical analyses. Molecular biological profiling with an adequate panel of carcinogenesis-related genes is currently considered to be an effective tool for a mechanistic approach to understanding lung cancer etiology. Such profiling of lung cancer among A-bomb survivors will be useful for better understanding of radiation carcinogenesis in the lung.

Hypothesis and specific aim: We hypothesize that the profile of genetic and/or epigenetic alterations in radiation-associated lung cancers among A-bomb survivors differs from that in sporadic (not radiation-associated) lung cancers. To test this hypothesis, we will analyze genetic and epigenetic alterations related to lung carcinogenesis using lung cancer tissue specimens obtained from A-bomb survivors.

Study design and methods: Samples to be used are archival lung cancer tissue specimens collected by the local pathologist network in Hiroshima and those stored at RERF. Using biological materials obtained from these tissues and epidemiological data from the Life Span Study, we will examine genetic and epigenetic alterations associated with lung carcinogenesis, and analyze associations between these molecular alterations and radiation dose in lung cancer as well as pre-cancerous lesions, considering 1) histological type (e.g., squamous cell carcinoma or adenocarcinoma) and grade of differentiation, and 2) smoking effects.

RP 2-13 Estimation of Genetic Risk of Radiation on Mature Oocytes of Mice by Using Next Generation Sequencer

Satoh Y, Furukawa K, Cullings HM, Nakamura N, Nishimura M, Shimada Y, Asakawa J

The genetic risk estimation of human radiation exposure has relied for the most part on mouse studies focusing on specific loci, although sensitivity varied from one locus to another. To better understand the mean mutation-induction rate per genome, a large number of genes per individual needs to be examined concurrently. For this purpose, we have examined radiation-induced mutation frequency by measuring deletions detected with two-dimensional gel electrophoresis, which scans some 1,000 loci, and high-density microarray comparative genome hybridization, which surveys approximately 70% of the genome. In this research protocol, we propose to conduct a detailed investigation by whole-genome sequencing of mouse parents and their offspring born to 4-Gy irradiated mature oocytes using next generation sequencing. We will clarify the mutation frequency and spectrum for small deletions/insertions, inversions, and translocations that are not detectable by the above-mentioned methods.

Recent Publications

(Japanese): the original article is in Japanese

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- Ohishi W, Cologne JB, Fujiwara S, Suzuki G, Hayashi T, Niwa Y, Akahoshi M, Ueda K, Tsuge M, Chayama K: Serum interleukin-6 associated with hepatocellular carcinoma risk: A nested case-control study. *Int J Cancer* 2014 (January); 134(1):154-63. (RERF Report 14-12)
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Publications Using RERF Data

The following publications represent research done by non-RERF scientists based on the data publicly available from RERF.

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