放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
Volume 23, Issue 2, 2012

Radiation Effects Research Foundation

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Cover photograph: Open House visitors examining blood cells through RERF microscopes. Related articles on pages 6 and 30.

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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.

Editor-in-Chief: *Evan B. Douple, Associate Chief of Research*
Technical Editor: *Fumie Maruyama, Public Relations & Publications Office*

Editorial Policy

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

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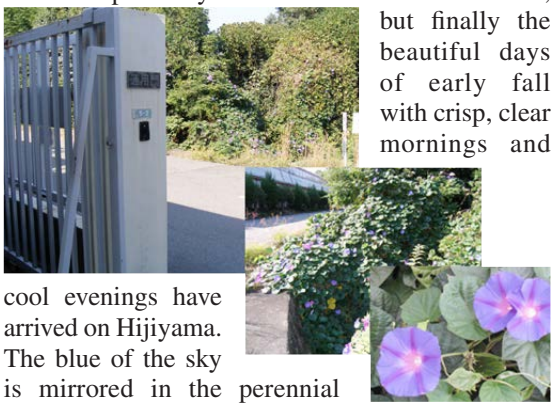
From the Editors

Welcome to *RERF Update*! It has been a long and exceptionally hot summer in Hiroshima, but finally the beautiful days of early fall with crisp, clear mornings and cool evenings have arrived on Hijiyama. The blue of the sky is mirrored in the perennial morning glories (*Ipomoea indica* [Merr.]) that greet RERF employees at the employee gate, and the maple leaves are finally turning red as the cool evenings signal that the transition from fall to winter will soon begin.



This issue of *Update* includes in **RERF News** a report on the second Board of Councilors meeting held in Washington, DC, in June. In July, RERF scientists continued to provide public lectures to serve citizens who continue to be concerned about the effects of radiation that may be relevant to those exposed during the Fukushima accident. August found RERF scientists working hard to provide an interesting and informative Open House in Hiroshima and Nagasaki (see cover photo) and more information about RERF's public relations activities is provided by Executive Director Takanobu Teramoto in **Facts and Figures**. In response to suggestions from advisory committees over the last few years that RERF should review the composition, research focus, and structuring of its basic science departments of Genetics and Radiobiology/Molecular Epidemiology (RME), a special international workshop was convened to assist RERF scientists in assessing their future plans and the future direction of RERF research. The workshop was titled "Future Plans and Structure for Research in the Basic Sciences at RERF" and a summary of the workshop is presented in **Conference and Workshop Reports**.

Two radiation effects about which RERF scientists have contributed important information over the years are cataracts and thyroid cancer. Please read the two **Science Articles** updating RERF's recent findings with respect to those two health effects. We received a nice letter of support from Mr. Kenji Joji (see **Letters to the Editors**) who also expressed his sorrow in reading about the deaths of some of ABCC-RERF's key leaders. In **Human Interest Notes** read more about the services held for the late Dr. Itsuzo Shigematsu and about the recent loss of a dedicated and long-time RERF pathologist, Dr. Shoji Tokuoka.

Dr. Roy E. Shore (far right) and Dr. Evan B. Douple (far left) host a visit by Dr. John O. Pastore, his wife, and his granddaughter (center, right to left)

It was a pleasant surprise in August when a former ABCC employee, Dr. John O. Pastore stopped to visit RERF accompanied by his wife and granddaughter. Dr. Pastore was assigned to ABCC as a physician by the U.S. Public Health Service. He served two years from 1969–1971 as an epidemiologist and clinician with an interest in cardiovascular disease and stomach cancer. Americans will probably recognize the name of Dr. Pastore's father (same name) who served as a distinguished U.S. Senator from Rhode Island for 26 years. Dr. Pastore was in Hiroshima as a participant in the 20th World Congress of the International Physicians for the Prevention of Nuclear War (see **RERF News)**. During his tour of RERF, Dr. Pastore recognized that his former office is now an ultrasonography exam room.

The other night a healthy tanuki (raccoon dog) family with two "youngsters" stopped by our kitchen window in Apartment E at Hijiyama Hall (RERF's housing) as if to say "What's for dinner?"—although they probably had just finished dining on Dr. Roy Shore's composting garden soil. Perhaps they were simply saying "sayonara" after hearing that I will be leaving Hiroshima in December to retirement and our home in Reston, Virginia. Yes—the last five years, 10 issues of *Update*, and many pleasant memories have seemed to pass rather quickly. My successor will find that Maruyama-san has the newsletter in good shape, but they both of course will welcome

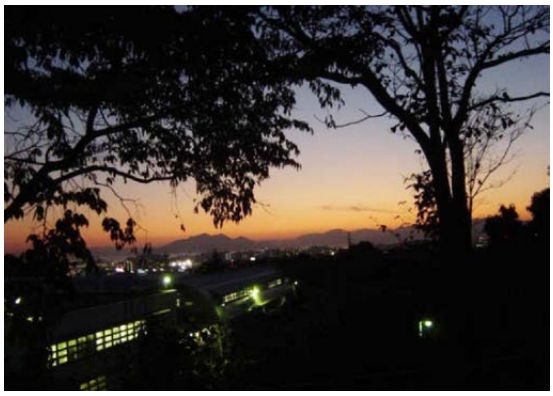
A tanuki visiting Hijiyama Hall

any feedback and suggestions for improvement that you may offer.

Mata oidekudasai (goodbye and please come again).

Evan B. Douple
Editor-in-Chief

Fumie Maruyama
Technical Editor



The lights of RERF and the sun setting over Miyajima Island viewed from an apartment in Hijiyama Hall

Brenda and Evan Douple exiting a temple gate

Letters to the Editors

Dear Maruyama-san,

Thank you very much for the recent issue of *RERF Update*, which served to bring me up to date on the developments at RERF, particularly its status as a public interest incorporated foundation in Japan on April 1, 2012.

Indeed, I have read your In Memoriam with sorrow and sympathy to the bereaved families of passing of Dr. Itsuzo Shigematsu who had the longest contributory tenure as RERF chairman, Dr. James Franklin Crow in his significant role in the Scientific Council of RERF and the Crow Committee, and Mr. Seymour Jablon, who essentially organized the Unified Study Program of ABCC, which employs among others the Japanese *koseki* system in the follow-up of the fixed study population of RERF.

Their immense contributions to the research program and its future are truly immeasurable. Yes, it was a great pleasure for me to have been able to work with them at ABCC and RERF.

I look forward with great pleasure and expectation to your competent role in the publication of *RERF Update* in the years to come.

The initiation of *RERF Update* by Ms. Beth Magura in 1989 is an event of great importance for the dissemination of the scientific research results of RERF for the organization itself and to the public at large. Fortunately, we still maintain congenial correspondence though a great deal of time has elapsed since she left her footprints at RERF.

Kindly extend my warmest regards to Dr. Evan B. Douple.

Gratefully yours,
Kenji Joji
July 14, 2012

The Second Board of Councilors Meeting Held in Washington, DC

The second meeting of the Board of Councilors was held on June 19 and 20 (U.S. time), 2012 at the National Academy of Sciences in Washington, DC. All Councilors as well as Directors, Auditors, and one of the co-chairs of the Scientific Advisory Committee attended the meeting, the first gathering since RERF made the transition to a public interest incorporated foundation. Officials of the U.S. and Japanese governments, the U.S. Department of State, and the National Academy of Sciences participated in the meeting as observers. Following the greetings by the representatives of both governments, the following items were deliberated.

The activities report, settlement of accounts report, audit reports, and auxiliary documents were presented to convey RERF's operational status for FY2011, and all were unanimously approved.

As was done last fiscal year, reports were made concerning FY2012 activity plans and budget-related matters, research projects on A-bomb survivors' health and on the health of A-bomb survivors' children, elucidation of individual radiation doses and the effects from A-bombs, release of research results and collaboration with other scientific organizations, training programs for domestic and overseas specialists, and public information programs, as well as research plans and working budgets necessary to conduct the projects and programs mentioned above. In addition, measures to cope with further unexpected appreciation of the yen were reviewed, and this year RERF's future plans and contributions related to the incident at the Fukushima Dai-ichi nuclear power plant were given special notice.

Dr. Sally A. Amundson, Co-chair of the Scientific Advisory Committee, reported that the committee conducted extensive reviews on the activities of the Departments of Radiobiology/Molecular Epidemiology and Genetics at its meeting held on March 5–7 at the Hiroshima Laboratory. She explained that three general recommendations (research prioritization, support activities for Fukushima, and preservation of biological samples) and other specific recommendations were made, after which RERF's responses to these recommendations were discussed.

Concerning procedures of the Board of Councilors, qualification requirements and appointment procedures of the Councilors, Directors, Auditors, Scientific Advisors, and Local Advisors were confirmed, and for smooth operation of the board, establishment of the Rules of Procedure of the Board of Councilors was discussed.

As for official actions related to directors and other officials, two Auditors and Dr. Michael N. Cornforth, Scientific Advisor, were reappointed. Dr. Yoichi Gondo (RIKEN) was appointed as Scientific Advisor to replace Dr. Katsushi Tokunaga.

List of Participants

Councilors:

Mr. Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal

Dr. Yasuhito Sasaki, Executive Director, Japan Radioisotope Association

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, Managing Director, Pew Health Group, The Pew Charitable Trusts

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-chairperson of Scientific Advisory Committee:

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

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. Ryo Takagi, 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. Joseph F. Weiss, Japan Program Manager, Office of Domestic and International Health Studies, Office of Health, Safety and Security, DOE
Mr. Jordan G. Heiber, Office of Japanese Affairs, U.S. Department of State
Dr. Warren R. Muir, Executive Director, Division on Earth and Life Studies, National Research Council (NRC), U.S. National Academy of Sciences (NAS)
Dr. Gregory H. Symmes, Deputy Executive Director, Division on Earth and Life Studies, NRC, NAS
Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS
Ms. Laura Llanos, Financial & Administrative Associate, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS

RERF:
Dr. Evan B. Douple, Associate Chief of Research
Mr. Eiji Akimoto, Chief of Secretariat
Mr. Douglas C. Solvie, Associate Chief of Secretariat

Participants of the second meeting of the Board of Councilors in front of the National Academy of Sciences

Local Liaison Council Meetings Held in Hiroshima and Nagasaki

The 18th meeting of the Hiroshima Local Liaison Council (HLLC) was held at the Hiroshima Laboratory on September 13, 2012. Of the 15 council members, 13 (including proxies) attended the meeting, which was chaired by HLLC chairman Dr. Toshimasa Asahara (President of Hiroshima University). To begin the meeting, RERF Chairman Toshiteru Okubo briefed the participants on the positioning of the council at RERF as the foundation completed its transition to a public interest incorporated foundation, and asked the council for its continued guidance in terms of RERF's operations. After greetings by HLLC chairman Asahara, the meeting's proceedings started with RERF's general report on progress made during the past year, including the formulation of RERF's Future Plans 2012, which contains a plan to establish a Biosample Center (tentative name), and assistance provided to the health management survey conducted by Fukushima Medical University. The summation was followed by reports on recent research activities and results, the clinical study of

second-generation A-bomb survivors, the status of collaborative study with the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and the foundation's public-relations activities. Council members made comments in response to the plan for centralized management of biosamples, and HLLC Chairman Asahara expressed his idea to initiate discussions with RERF on biosample data sharing in light of the importance of promptly feeding back RERF's research results to the A-bomb survivors.

The 21st meeting of the Nagasaki Local Liaison Council (NLLC) was held at the Nagasaki Laboratory on October 11, 2012, and 17 (including proxies) out of 20 council members participated. After Dr. Okubo's greetings, the session's proceedings got underway, with Dr. Shigeru Katamine, NLLC chairman and President of Nagasaki University, presiding over the meeting. RERF's representatives made the same reports at the meeting that they did in Hiroshima on the foundation's present status and recent progress. Questions were asked, opinions actively exchanged, and valuable comments made concerning the plan to establish the biosample center, the data that RERF possesses, and the clinical follow-up study of the second-generation A-bomb survivors. Lastly, Dr. Katamine requested RERF to fully consider the discussions made at the meeting and incorporate them in RERF's operations, while referring to NLLC's role in collecting and conveying requests from the local community so that they are incorporated into RERF's activities. With this, the 21st meeting of the Nagasaki Local Liaison Council concluded.

The 18th Hiroshima Local Liaison Council meeting

Chairman Toshiteru Okubo Takes Office as HICARE President

On June 21, 2012, Chairman Toshiteru Okubo assumed office as President of the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE). He succeeded Dr. Shizuteru Usui (President of the Hiroshima Prefectural Medical Association), who passed away on May 9. The term of office is two years. Dr. Okubo had served as Director of HICARE for seven years since he assumed the chairmanship of RERF in July 2005.

Prompted mainly by the Chernobyl nuclear power plant accident, HICARE was established in 1991. The late Dr. Itsuzo Shigematsu, then RERF Chairman, was the first President of HICARE. HICARE is jointly operated by Hiroshima University (Faculty of Medicine, Hospital, and Research Institute for Radiation Biology and Medicine), the Hiroshima Atomic Bomb Casualty Council, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima A-bomb Survivors Relief Foundation, and RERF among others, with support from Hiroshima Prefecture, Hiroshima City, the Hiroshima Prefectural Medical Association, and Hiroshima City Medical Association.

HICARE is actively involved in a wide range of international collaborations. Among such activities are conveying of Hiroshima's accumulated knowledge about medical care for the radiation-exposed by accepting overseas medical personnel for training in medical treatment of the radiation-exposed, sending of medical specialists from Hiroshima to different regions throughout the world, and organizing lecture meetings and publishing manuals describing medical treatment of the A-bomb survivors. As for domestic activities, HICARE dispatched specialists to affected areas at the time of the criticality accident in Tokaimura (Ibaraki prefecture) in 1999 as well as the Fukushima Dai-ichi nuclear power plant accident in March 2011.

In recognition of its activities, HICARE received the 48th Health Culture Award in 1996 and both the 63rd Chugoku Shimbun Culture Award and the Foreign Minister's Award in 2006.

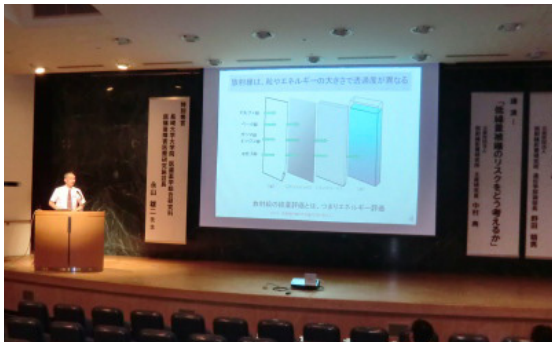
The Second Public Lecture Program for Citizens Held in Nagasaki

RERF held its second public lecture for Nagasaki citizens at a hall in the Nagasaki A-bomb Museum, from 1:30 to 4:00 in the afternoon of July 21 (Sat.). This open lecture program for citizens was carried out for the second time in Nagasaki to promote exchange between citizens and RERF staff, by providing intelligible explanations to the general public including A-bomb survivors on RERF's longstanding research achievements concerning A-bomb radiation health effects. Despite the rainy weather, more than 110 people attended the event.

The public event consisted of two lectures. First, Dr. Nori Nakamura (Chief Scientist) spoke on "Thinking about low-dose radiation exposure," explaining the level of risk increase due to radiation exposure using results from RERF's longitudinal studies of radiation health effects. Next, Dr. Asao Noda (Assistant Chief, Department of Genetics) gave a lecture titled "Methods for radiation dose assessment," introducing basic knowledge of radiation in a clear and straightforward manner and explaining that our fear of radiation should be appropriately based on an accurate understanding of radiation and its interactions in people.

At the beginning of the program, following greetings by Chairman Toshiteru Okubo, Ms. Sakue Shimohira, former President of the Association of A-bomb Bereaved Families in Nagasaki, shared her unhappy memories from the ABCC era as well as her relief about being able to undergo health examinations since ABCC's reorganization into RERF. She also expressed her high expectations for RERF's continued great success.

Dr. Yuji Nagayama, Director of the Atomic Bomb Disease Institute (ABDI), Nagasaki University Graduate School of Biomedical Sciences, gave feedback on the two lectures and made special remarks about the relationship between ABDI and RERF. In the Q&A session that followed, many questions were raised including those about internal and external exposures associated with the nuclear power plant events in Fukushima.



Second public lecture program for citizens held in Nagasaki

Open House Events in Hiroshima and Nagasaki

RERF held its Open House 2012 events on August 5 and 6 in Hiroshima and on August 8 and 9 in Nagasaki under the theme "Useful Knowledge about Radiation and Health Sciences." They were the 18th and 16th such events in Hiroshima and Nagasaki, respectively.

The Hiroshima Laboratory hosted a special exhibit on effects of low-dose exposure as well as a feature exhibit titled "Hiroshima and Nagasaki after the atomic bombings and in recovery" showing photos taken by Dr. Paul Henshaw and documentary footage of Hiroshima recovering from the devastation. The specialist's corner next to the special exhibit was visited by many guests who asked questions about radiation. A lecture commemorating 65 years of ABCC-RERF titled "Radiation exposure health risks and Fukushima" and one titled "What is radiation?" were given by Dr. Toshiteru Okubo, RERF Chairman, and Dr. Norio Takahashi, a senior research scientist at the Department of Radiobiology/Molecular Epidemiology, on August 5 and 6, respectively. The research departments displayed exhibits introducing their respective studies conducted with the support and coop-

A lecture commemorating 65 years of ABCC-RERF given by RERF Chairman Toshiteru Okubo for the Hiroshima Open House

eration from A-bomb survivors and many others. Over the event's two days, the Hiroshima Laboratory drew 964 visitors eager to listen to the exhibit explanations and lectures.

In Nagasaki, in addition to the conventional exhibits showing RERF's research methods and achievements, this year's Open House included a special exhibit in which health risks from low-dose radiation exposure were explained visually with diagrams, and the same feature exhibit of photographs taken by Dr. Paul Henshaw used in Hiroshima also were on display. Unlike in typical years, the hands-on exhibits were not crowded with participants this year, making it possible for RERF staff to devote substantial time to engaging with guests. Over the event's two days, the Nagasaki Laboratory drew 326 visitors.

Open House at the Nagasaki Laboratory. Epidemiology Department Chief Kotaro Ozasa (center) is explaining radiation health risks to the visitors.

IPPNW Participants Visit RERF

On the morning of August 23, eight participants in the 20th World Congress of the International Physicians for the Prevention of Nuclear War (IPPNW) visited RERF Hiroshima Laboratory. The congress was held on August 24–26 at the International Conference Center Hiroshima. After being greeted by Chairman Toshiteru Okubo, the visitors listened to lectures by Dr. Kotaro Ozasa (Chief, Department of Epidemiology; "Cancer risk of A-bomb survivors"), Dr. Nori Nakamura (Chief Scientist; "Genetic effects of A-bomb survivors"), Dr. Harry M. Cullings (Chief, Department of Statistics; "Dosimetry of A-bomb survivors"), and Dr. Kazunori Kodama (Chief Scientist; "Radiation health effects and nuclear abolition"). After the lectures, they were shown panels introducing the history of ABCC and RERF, which Dr. Kazunori Kodama explained. They then received explanations by Dr. Yoshiaki Kodama (Chief, Department of Genetics) about biodosimetry and by Dr. Yoichiro Kusunoki (Chief, Department of Radiobiology/Molecular Epidemiology) about the mechanistic study of radiation effects in each department.

IPPNW was founded in 1980 with headquarters in the U.S. state of Massachusetts. IPPNW aims to prevent nuclear war by disseminating accurate knowledge and information on medical effects caused by such conflicts from the perspective of physicians with the responsibility to protect people's lives and health. IPPNW was awarded the 1985 Nobel Peace Prize. The IPPNW World Congress this past August was held in Hiroshima for the first time in 23 years. At the session "Educational Lecture on Health Effects of Radiation," which was open to the general public, Vice Chairman Roy E. Shore delivered a talk titled "Health effects from radiation exposure" on August 25. At that lecture session, Dr. Kazunori Kodama served as co-chair.

Chairman Toshiteru Okubo (far right) briefing the visitors from the IPPNW World Congress

Visiting Scientists

RERF was fortunate to have several former RERF scientists visiting Hiroshima this fall. Two former chiefs of the Statistics Department, Dr. **Dale Preston**, Chief Scientist in the HiroSoft International Corporation, and Dr. **Donald Pierce**, a professor in the Oregon Health and Science University, were back at RERF where they were working for a little over two weeks on several projects including a contract with the U.S. National Cancer Institute (NCI). Another Department of Statistics Consultant, Dr. **Daniel Stram**, another former RERF statistician and currently a professor in the Department of Preventive Medicine, University of Southern California, also spent a few days and presented a lecture titled "Analysis of cancer risks in populations near nuclear facilities: Phase I."

Déjà vu—Donald Pierce (left) and Dale Preston hard at work as if it was a previous time at RERF.

Staff News

Three department chiefs reached mandatory retirement age and were reappointed effective June 30, 2012; **Masazumi Akahoshi**, Chief of the Department of Clinical Studies, Nagasaki, **Harry M. Cullings**, Chief of the Department of Statistics, and **Hiroaki Katayama**, Chief of the Department of Information Technology. **Wan-Ling Hsu**, resigned effective September 10 as an Associate Senior Scientist in the Department of Statistics. She moved to Shanghai, China to join her family. **Nori Nakamura**, a Chief Scientist, resigned effective December 31 and will be appointed as a Consultant to the Department of Genetics effective January 1, 2013. **Evan B. Douple**, Associate Chief of Research, resigned effective December 31. He will return to the U.S. where he will retire.

Norio Takahashi's term as Senior Scientist in the Department of Radiobiology/Molecular Epidemiology expired on October 31, 2012 and he was assigned as a Consultant to the Vice Chairman's Office effective November 1. **Hiromi Sugiyama**, Associate Senior Scientist, was promoted to Acting Office Chief of the Tumor and Tissue Registry Office in the Department of Epidemiology as of October 1. And on a final note, **Atsuko Sadakane** (MD, PhD) was recruited and appointed as an Associate Senior Scientist in the Department of Epidemiology as of October 1. Her research interests are the Life Span Study in RERF and the epidemiology of cancer and noncancer diseases. Her self-introduction follows.

Atsuko Sadakane, MD, PhD

Atsuko Sadakane

I joined the Department of Epidemiology in Hiroshima as a research scientist on October 1. I graduated from Jichi Medical University in Tochigi prefecture in 1999. Jichi Medical University was established jointly by Japan's prefectural governments to train physicians who can contribute to improving health and welfare in medically disadvantaged communities. Only a few students from each prefecture enter Jichi Medical University every year. All students are exempted from tuition costs on the condition that they work after graduation in medically disadvantaged areas of the prefecture they come from for a certain period of time. In keeping with the spirit of establishment of the university, I worked at a clinic on a remote island and other places in Fukuoka prefecture after graduation.

In 2008, after having spent nine years as a clinician, I joined the Department of Public Health at Jichi Medical University's Center for Community Medicine, where I engaged in educational and research programs in epidemiology and public health. I first set my sights on epidemiological research because of my involvement in a baseline investigation for a cohort study immediately after entering the university, interest in the field generated by an epidemiology class I took in my junior

year of the university, and the fact that the region where I worked as a physician was being studied as part of an epidemiological project.

I am honored to have the opportunity to carry out as a research scientist the research mission of RERF, an organization with a long history and unique character. It will take some time before I am able to achieve my goal of contributing to RERF's future. I want to begin, however, by learning about the histories of RERF, Hiroshima, and Nagasaki and understanding RERF's research achievements.

Reflecting on my situation now, I have had some connections with Hiroshima in my life. First, my wedding was held in Hiroshima nine years ago. And second, my husband started working in Hiroshima three years ago. People at RERF have been warm and kind ever since I applied for this job. With their help, I have been able to get off to a good start. I would like to get to know everyone at RERF as soon as possible. I look forward to receiving everyone's advice and guidance in my research activities. Thank you in advance for your support.

Awards Received by RERF Scientists

Receiving the 27th Prevention Award of the Japanese Association for Cerebro-cardiovascular Disease Control/Japan Heart Foundation

Kazunori Kodama, Chief Scientist

On June 15, 2012, at the 48th annual scientific meeting on cardiovascular disease prevention of the Japanese Association for Cerebro-cardiovascular Disease Control (JACD) held in Tokyo, I was presented with the JACD/Japan Heart Foundation's Prevention Award.

The award is presented to researchers who have contributed to the prevention of stroke and heart disease in Japan, with this year marking the 27th such presentation. I was bestowed the honor for my contribution to the promotion of epidemiological research on circulatory diseases in Hiroshima and Nagasaki and in the NI-HON-SAN study, and for the education and training of young researchers at seminars on prevention of circulatory diseases in Japan. This was my second time to receive the award, my first being the 7th such award in 1992 for epidemiological research on circulatory diseases. I have to believe I received the award this time for my contribution in particular to the aforementioned seminars on prevention of circulatory diseases in Japan.

Kazunori Kodama, Chief Scientist, with his award

The seminars were initiated in 1988 in the form of a five-day camp, with a view to cultivating young researchers capable of being active on the front lines in the field of circulatory disease prevention, and have been held in turns mainly in the regions where circulatory disease prevention studies are conducted. This year marked the 25th seminar, and more than 1,000 physicians, medical students, and allied health professionals have participated to date, with many becoming mainstays in research and activities related to prevention of circulatory diseases in Japan.

I was involved in the 1st through the 20th seminars as a member of its executive committee and in the 22nd through the 24th seminars as a lecturer. This means that I participated in 23 seminars out of the total of 25. I also organized and convened the 5th seminar in Hiroshima. Being the oldest member in the seminar series, I suspect that JACD, in granting the award to me, had the ulterior motive of suggesting that it is about time for me to retire.

Fortunately, younger members have been trained and are competent and active enough to take over the reins, and taking this opportunity, I have announced my resignation. For everyone's reference, Dr. Itsuzo Shigematsu was involved in JACD's establishment in 1965. I truly wish he was alive today, as he surely would have been very pleased to hear this news.

Receiving the Third Hypertension Research Award

Ikuno Takahashi, Research Scientist
Department of Clinical Studies, Hiroshima

At the 35th annual scientific meeting of the Japanese Society of Hypertension (JSH), held in Nagoya during the period September 20–22, 2012, I was presented with the third Hypertension Research Award. The award was established by the JSH in 2010 to honor researchers who have published papers in the JSH's journal *Hypertension Research* during the past one year and contributed to hypertension research and the Society's development and advancement.

My award-winning paper was selected from among papers published in *Hypertension Research* between April 2011 and March 2012. Titled "Lifetime risk of stroke and impact of hypertension: Estimates from the Adult Health Study in Hiroshima and Nagasaki" (*Hypertens Res* 2011; 34:649–54), the paper examined the risk of stroke and reported on long-term effects of hypertension on stroke risk based on RERF's Adult Health Study (AHS).

Determining the level of long-term contribution of certain risk factors (e.g., hypertension) to the development of diseases such as stroke serves as important evidence in decision-making related to therapeutic strategies regarding such issues as what conditions should be treated how aggressively for what types of people in order to prevent serious diseases. However, this kind of evidence was nearly nonexistent before the paper was published. This probably explains why my paper has received such recognition.

Since I joined RERF in Hiroshima six years ago, I have been investigating effects of radiation exposure on stroke incidence, and reported the possibility of differences in radiation effects by stroke subtype starting with the recent paper that won the award. The study also has led to other studies that I am now conducting of arteriosclerosis and circulatory diseases. The paper that marked the beginning of my present research could not have received the award, however, without the cooperation of the AHS participants as well as support from the staff of the Departments of Clinical Studies in Hiroshima and Nagasaki, Statistics, Epidemiology, and Information Technology, as well as many others, and for that I am truly grateful to them. I also received generous guidance and support in conducting the study and writing the manuscript from Dr. Saeko Fujiwara, chief of the Department of Clinical Studies when the manuscript was written, and Dr. Masayasu Matsumoto, professor at the Hiroshima University Department of Clinical Neuroscience and Therapeutics. I would like to take this opportunity to express my sincere appreciation to all of them.

Ikuno Takahashi, Research Scientist, with her award

I am determined to push ahead in order to achieve the goals of assessing radiation risk of circulatory diseases and elucidating mechanism(s) underlying the development of such disease. With that in mind, I look to you all for your continued guidance and encouragement.

(Editor's note: A summary of Dr. Takahashi's award-winning article appears in the Science Articles section of Volume 22, Issue 2, 2011, of *RERF Update*.)

Upon Receiving Encouragement Award for Medical Research from the Japan Medical Association

Waka Ohishi, Acting Chief
Department of Clinical Studies, Hiroshima

I recently received the 2012 Encouragement Award for Medical Research at the 65th Anniversary Convention of the Japan Medical Association (JMA) held at the Nihon Ishi Kaikan in Tokyo on November 1, 2012. This award is presented to a researcher younger than 50 years of age conducting promising medical research, and my award-winning research theme was "Identification of biomarkers contributing to risk for hepatocellular carcinoma development and the biomarkers' usefulness."

I was hired by the Radiation Effects Research Foundation (RERF) in 2004, and what paved the way to my career here was the joint research project "A nested case-control study of hepatocellular carcinoma among atomic-bomb survivors using stored sera" initiated by Dr. Saeko Fujiwara, for-

mer chief of the Clinical Studies Department, and Dr. Kazuaki Chayama, professor of gastroenterology and metabolism and Director of Hiroshima University Hospital. Right away, I was moved to learn that the sera obtained from the people who have participated in our Adult Health Study over so many years had been stored since 1969, and at the same time I started thinking daily on a trial-and-error basis about methods regarding how such valuable serum samples could be utilized. Fortunately, thanks to the full support I received from the staff of the Clinical Laboratories Division, I was able to prepare a protocol on use of the stored sera based on compiled materials related to serum storage methods and thereby proceed smoothly with review of the fundamentals of the process.

I first reported in *J Clin Microbiol* (44:4593–5, 2006) that use of stored sera would not be a problem for detection of hepatitis virus, and I also reviewed the possibility of using such sera in terms of other examination items (total protein, total cholesterol, fibrosis marker, C-reactive protein, etc.). Based on these specific reviews, I reported in *Cancer Epidemiol Biomarkers Prev* (17:846–54, 2008) and *Hepatology* (53:1237–45, 2011) that hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol consumption of more than 40 g per day, obesity with a body mass index (BMI) of 25 kg/m^2 or more, and radiation exposure were all independent risk factors for hepatocellular carcinoma.

I believe I was presented with the aforementioned award for my series of past studies and ongoing project on biomarkers involved in the risk of hepatocellular carcinoma. I would like to take this opportunity to sincerely thank Drs. Saeko Fujiwara, John Cologne, Gen Suzuki, and Kazuaki Chayama for their guidance and cooperation in initiating the research using the valuable stored sera, which represent very important assets for RERF; the staff of the Departments of Clinical Studies and Epidemiology in both Hiroshima and Nagasaki, as well as Hiroshima's Departments of Statistics and Information Technology, for their comprehensive support; and the staff of the Departments of Genetics and Radiobiology/Molecular Epidemiology for their generous technical advice. Finally, I would like to conclude this article by expressing heartfelt gratitude to Chairman Toshiteru Okubo for providing me with the chance to apply for this prestigious award, and by asking for everyone's continued guidance and support.

Waka Ohishi, Acting Department Chief, with her award

Future Plans and Structure for Research in the Basic Sciences at RERF
A Summary of a Workshop Held at the Radiation Effects Research Foundation, March 8, 2012

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

During the past few years, RERF's scientific advisory bodies have pointed out that the departmental structure of RERF's basic science research, primarily the Department of Genetics and the Department of Radiobiology/Molecular Epidemiology (RME), have not changed for quite some time. They encouraged RERF to assess the effectiveness of the current structuring, appraise and prioritize the current major areas of research, and identify areas of expertise where future recruitments of younger scientists might have a significant and immediate impact on the research themes of RERF. Seven researchers distinguished in the areas of genetics, radiobiology, and molecular epidemiology research were invited to participate in a half-day workshop to assist RERF scientists in their review of the RERF basic science research. The workshop was divided into five sessions. The

sessions are described below and the session moderators are identified in parentheses. Fourteen major recommendations are numbered and summarized in bold.

I. Introduction, Goals, and Charge (Toshiteru Okubo/Roy E. Shore)

The RERF Chairman and Vice Chairman asked participants to think about the future of RERF basic science research, specifically with respect to the two departments of Genetics and RME. This is especially important since: (a) RERF has been requested to develop long-term future plans; (b) a significant number of research scientists are reaching or have reached retirement age; and (c) tight budgets require that we prioritize what recruitments should be conducted and what basic science research should and could be done within the context of our mission and the interests of the supporting governments. Other key questions raised included: (d) Should RERF continue to have two separate departments with the current structure? (e) How competitive is RERF research in a global sense?, and (f) What and how can we do better than others?

The RERF Chairman concluded his remarks by pointing out that answers to the above questions and critical judgments are difficult to make within the organization so RERF appreciates having the outside advice and perspectives that the participants brought to this workshop.

II. Future of the Genetics Department: Perspectives and Plans (Katsushi Tokunaga/ John J. Mulvihill)

The Chief of the Genetics Department, Dr. Yoshiaki Kodama, summarized the department's future plans, key recruitment and facility needs, and thoughts regarding department reorganization. The focus of research proposed included: (a) Estimation of the genetic effects of A-bomb radiation in humans using the whole-genome sequencing-based approach; (b) Use of the green fluorescent protein (GFP) mouse model to study somatic and germline mutations *in situ*; and (c) Development of new methods for biological dosimetry (flow-fluorescence *in situ* hybridization [FISH]). With respect to recruitment needs, Dr. Y. Kodama recommended and prioritized three desired recruitments: (a) A bioinformatician to assist with the design, interpretation, and analyses of experiments; (b) A young scientist with animal model experience; and (c) A young scientist with an interest in biodosimetry and molecular biology. With respect to facilities that would assist the department research scientists in meeting their goals, Dr. Y. Kodama cited a next-generation sequencer five years from now, an improved animal facility as soon as possible, and a state-of-the-art flow cytometer. With respect to the department members' reaction to the proposed options for departmental reorganization, the department members supported investigating some form of restructuring of the two departments and recruitment of a department chief.

1. **Understanding the effect of radiation on the human genome remains an important challenge and RERF has precious biosamples to help mankind learn how sensitive the genome is to radiation and how much genomic variation affects the transport of radiation risk from RERF to other populations.**
2. **While RERF should consider the use of next-generation whole genome sequencing, it is expensive, requires high-level bioinformatics expertise for interpretation of results, might not be able to resolve key questions related to mechanisms of mutation and other radiation effects, and may have to involve collaborations and outsourcing external to RERF; planning an international workshop might be considered to provide assistance and advice in this issue.**
3. **Developing new biodosimetric techniques such as flow-FISH is interesting, but might not be the best use of RERF resources; however, it is to RERF's advantage to maintain cytogenetic capability because of potential societal needs.**
4. **The model in which mutant cells become green because of expression of GFP is especially interesting and should be expanded to include *in vitro* irradiation studies which correlate with the GFP mouse data.**

III. Future of the RME Department: Perspectives and Plans (Sally A. Amundson/ Kazuo Sakai)

The session was opened with a statement by the Chief of the RME Department, Dr. Yoichiro Kusunoki, who summarized the department's future plans, key recruitment and facility needs, and thoughts regarding department reorganization. The focus of research proposed included: (a) Risk assessments of radiation- and aging-related diseases; (b) Mechanistic studies of radiation-induced carcinogenesis; and (c) Mechanistic studies of radiation-associated noncancer diseases. With respect to recruitment needs, Dr. Kusunoki recommended and prioritized two desired recruitments—a mid-career scientist with expertise in new analytical technologies who would be qualified to take leadership in the Cell Biology Laboratory and a young

scientist with immunology training and research interests. With respect to facilities that would assist the department research scientists in meeting their goals, Dr. Kusunoki cited a next-generation sequencer five years from now, an improved animal facility as soon as possible, and a state-of-the-art flow cytometer. The latter equipment could be used in combination with mass spectrometry to facilitate the measurement of protein expression levels and studies of proteomics and metabolomics, and could be used in RERF's studies of epigenetics. With respect to the department members' reaction to options for departmental reorganization, the department members supported an attempt to restructure the two departments.

5. **Studies of methylation and epigenetic effects represent important topics for RERF research, but clearly defined hypotheses need to be articulated for those studies to be productive and meaningful.**
6. **RERF scientists working on using archival tissues for cancer studies were encouraged to collaborate with Dr. M. Atkinson's group in Germany who have been extracting DNA from archival tissues.**
7. **The studies of the involvement of specific chromosomal translocations such as with *RET* and *ALK* genes are important since they may explain individual differences in radiation susceptibility.**

IV. Basic Science Restructuring Options (Evan B. Douple/Kazunori Kodama)

Dr. Evan Douple discussed various considerations regarding restructuring the basic science departments. He pointed out that the three key ingredients that require decisions to be made and which rely on each other are: (a) Plans for future research directions; (b) Recruitment of new scientists to carry out those plans; and (c) Restructuring of departments to optimize shared resources, expertise, and new ideas. He pointed out that RERF scientists have been requested to prepare long-range plans for the foundation and it will be necessary to decide whether and how many scientists should be recruited to fill future anticipated vacancies, and whether certain projects can be done at RERF or whether it is more effective to outsource certain tasks and establish collaborations with scientists outside RERF. Of course another alternative is to continue current research activities and essentially proceed as the status quo.

With respect to recruitment, Dr. Douple raised the following questions:

a. What kind of scientists should we recruit (young, mid-career, or established)?
b. Do we have the appropriate department structure to provide younger scientists with requisite mentorship?
c. Do we know what we want the scientists to be able to do?
d. How best can we get the message out that RERF is recruiting scientists?
e. Are there qualified candidates who might be interested in RERF and available?
f. Can we successfully recruit highly qualified candidates to come to RERF?

The session concluded with a discussion focused on five restructuring scenarios. It was generally agreed that RERF should not take the option to dissolve the Genetics Department. RERF needs genetic expertise, geneticists need to resolve the radiation mutation risk in humans, the A-bomb dosimetry may benefit some from cytogenetic studies and electron spin resonance (ESR) tooth dosimetry, and despite a large percentage of scientists who have reached retirement age a core will remain who are working on promising projects. With respect to the option to restructure Genetics and RME, one possible change would be to update the names of the laboratories.

8. **Both basic science research departments at RERF would benefit from an improved animal facility since mouse studies are important to bridge the epidemiologic findings to basic biology and humans.**
9. **It was suggested that departmental laboratory delineations, if retained, be renamed with more up-to-date terminology (cytogenetics→cellular genetics; biochemical genetics→molecular genetics; immunology→radiation immunobiology; cell biology→molecular oncology or molecular epidemiology.**
10. **If the two basic science departments were merged, it would encourage collaboration and sharing of new technologies, possibly lead to more cutting-edge research, and could include working groups with the potential to promote cross-fertilization and creativity; such a merger might be called Department of Radiation Biology and Genomics.**
11. **Final administrative decisions regarding retention of the existing departments or restructuring should depend on the prioritization of the future research and recruitment plans.**

V. General Discussion and Recommendations Regarding Future Directions and Structure (Kiyoshi Miyagawa/William F. Morgan)

A. Future Directions: It was stated that basic sciences will become more important in the future,

because clinical and epidemiological studies will be reduced due to the deceased cohort. It was emphasized that the primary research issues for basic science research are to provide a bridge to the Epidemiology, Clinical Studies, and Statistics Departments, so that the epidemiologic study results regarding radiation risk can be better understood biologically. For example, an important issue is: What is the biological basis as to why exposure at younger ages gives a higher risk for some tissues but not for others? Another example is that it is important to bring basic studies to bear on how to reduce the confidence intervals (i.e., increase the precision of knowledge) regarding low-dose radiation risk. This requires mutual feedback and ideas among scientists. A third example is that the understanding about chromosome rearrangements in radiogenic thyroid cancer may provide an avenue for better understanding the effect. It was generally agreed that four major issues RERF scientists should and could address further were: age dependency, cancer-site specificity, effects at low doses/dose-rates, and transgenerational risk.

B. Communication Network: RERF should be more aware of and responsive to the needs of radiation science by developing as much discussion as possible with the outside radiation community. RERF scientists should look for opportunities for presenting their data to additional potential sources of funding including various divisions of the U.S. National Institutes of Health.

C. Recruitment: It was opined that scientific societies of molecular biology, human genetics, and bioinformatics know virtually nothing about the past/present research and research opportunities at RERF. Developing contacts and advertising positions in those venues would be valuable. However, RERF was cautioned to be realistic about funding and future recruitments and not aim for something we cannot achieve. It was suggested that RERF make a prioritized "wish list" of research areas in which we would like to recruit and think of places to advertise for those specialties. It was suggested that we try to work out a joint appointment with a university; this could make the recruitment package very attractive.

D. Restructuring Options: It was proposed that RERF consider organizing into two divisions to gain economies of scale; the two divisions would be clinical and epidemiological sciences, and laboratory sciences and core facilities. It was suggested that by combining two basic science departments RERF might save on administrative staff, but investigators were concerned about this idea because the staff are already overworked and this could compound the problem. There was some concern about future directions for cytogenetics and biodosimetry. However, it is important to maintain cytogenetic capabilities because of potential societal need, but obtaining external funding for research in this area is extremely difficult, thereby making it a difficult career decision for a young researcher. The workshop's concluding remark was that centralization of the biosample database is more important than centralization of collected cells. Comprehensive, accurate tracking of what has been done with given samples and what samples are available for future studies are what are most important.

12. **Since there will be multiple RERF research scientists retiring in the near future, a recruitment package might be made more attractive by permitting the recruit to bring a colleague and by providing a joint academic appointment with a university.**
13. **Key issues for future RERF radiation health effects research should include the (a) age dependency, (b) cancer-site specificity, (c) effects of low doses and dose rates, (d) role of somatic mutations, epigenetics and chromosome rearrangements in radiogenic cancers, (e) why exposure at younger ages give higher risks for some tissues but not for others, and (f) the estimation of transgenerational risk.**
14. **A high priority should be given to the establishment of a comprehensive, accurate, secure, and readily accessible centralized biosample database that might also be administered and monitored in a centralized biosample repository.**

Participants

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

Dr. Kiyoshi Miyagawa, Professor, Laboratory of Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo

Dr. William F. Morgan, Director of Radiation Biology and Biophysics, Biological Sciences Division, Pacific Northwest National Laboratory

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

Dr. Tetsuya Ono, Professor, Division of Genome and Radiation Biology, Department of Cell Biology, Graduate School of Medicine, Medical Sciences, Tohoku University

Dr. Kazuo Sakai, Director, Research Center for Radiation Protection, National Institute of Radiological Sciences
Dr. Katsushi Tokunaga, Professor, Department of Human Genetics, Division of International Health, Graduate School of Medicine, The University of Tokyo

RERF
Dr. Toshiteru Okubo, Chairman/Representative Director
Dr. Roy E. Shore, Vice Chairman and Executive Director
Mr. Takanobu Teramoto, Executive Director
Dr. Evan B. Douple, Associate Chief of Research
Dr. Nori Nakamura, Chief Scientist
Dr. Kazunori Kodama, Chief Scientist
Dr. Yoshiaki Kodama, Chief, Department of Genetics
Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology

Participants of the meeting on future plans and structure for research in the basic sciences at RERF

The 35th Meeting of the Japanese Society of Cancer Epidemiology

Kotaro Ozasa, President of the 35th meeting (Chief, Department of Epidemiology)

The 35th meeting of the Japanese Society of Cancer Epidemiology, based on the theme "Radiation and Cancer," was held on July 5 and 6, 2012, at the Aster Plaza (Naka-ku, Hiroshima). This society was established in July 2010 by the merger of the Japanese Society of Cancer Epidemiology and the Japanese Society of Cancer Molecular Epidemiology. The Japanese Society of Cancer Epidemiology held its inaugural general meeting in 1977, gathering research scientists who played key roles in the field of cancer epidemiology in Japan. Dr. Hiroo Kato, RERF, and Dr. Noboru Kurihara, Hiroshima University, jointly took charge of the 5th meeting, which was held in 1982. The 18th meeting was held in 1995 under the presidency of Dr. Kiyohiko Mabuchi. On the other hand, the Japanese Society of Cancer Molecular Epidemiology was established to focus on molecular epidemiology in the field of cancer epidemiology, with its initial meeting held in 2000. The 4th and 7th meetings were held with Dr. Kei Nakachi at the helm in 2003 and 2006, respectively. Molecular epidemiology thereafter became a universal presence in the field of cancer epidemiology, and hence the two societies were merged as mentioned above. The combined society covers a broad range of fields that employ

epidemiology and molecular epidemiology with the aim of cancer prevention/treatment and acquisition of cancer-related information, such as descriptive epidemiology, analytic epidemiology, intervention research, cancer registry, health examination, molecular epidemiology, pathogenesis, diagnostic classification, incidence factors, preventive factors, prognosis factors, cancer management, cancer prevention, patient quality of life (QOL) issues, social systems, and other research areas.

The recent meeting introduced epidemiological research in Japan regarding radiation-cancer association from various perspectives with reference to the course of events following last year's TEPCO Dai-ichi nuclear power plant accident at Fukushima, explained principles of perception of radiation risk and related scientific findings, and offered an opportunity to review measures to deal with the current situation in Fukushima from an epidemiological viewpoint, incorporating the program indicated below:

Special lecture: "Major epidemiological studies of cancer risk and low-dose radiation" (Suminori Akiba, Kagoshima University)

Symposium: "Current status of radiation cancer epidemiology with special reference to low-dose risk"

- Epidemiological study of A-bomb survivors and challenges in low-dose risk assessment (Kotaro Ozasa, RERF)
- Mortality follow-up study of nuclear power plant workers (Fumiyoshi Kasagi, Radiation Effects Association)
- Study of potential radiation risk among residents in the vicinity of nuclear power plants (Yasuhiko Yoshimoto, National Institute of Radiological Sciences)
- Mortality follow-up study of radiology technicians (Shinji Yoshinaga, National Institute of Radiological Sciences)
- Radiation, smoking, and lung cancer (Kyoji Furukawa, RERF)
- Radiation risk of skin cancer among A-bomb survivors (Hiromi Sugiyama, RERF)

Workshop: "Health management after the Fukushima Dai-ichi nuclear power plant accident"

- Health management of residents in Fukushima prefecture (Seiji Yasumura, Fukushima Medical University)
- Health management of emergency/recovery workers (Shinji Yoshinaga, National Institute of Radiological Sciences)

Symposium: "Radiation and cancer molecular epidemiology"

- Molecular epidemiology of radiation-associated cancer (Tomonori Hayashi, RERF)
- Study of cancer in relation to gene-environment interaction, and case-cohort design (John B. Cologne, RERF)
- Molecular patho-epidemiological study based on stored solid cancer specimens from A-bomb survivors (Masahiro Nakashima, Nagasaki University)
- Characteristics of gene mutation in papillary thyroid cancer among A-bomb survivors (Kiyohiro Hamatani, RERF)
- Radiation-induced cancer and chromosome aberration (Satoshi Tashiro, Hiroshima University)
- Genetic effects from radiation among children of A-bomb survivors (Jun-ichi Asakawa, RERF)

Numerous RERF research scientists, symbolizing RERF's significance in the radiation epidemiology research community in Japan, served as lecturers at the meeting. Seventeen poster presentations also were made. The society is a small study group consisting of about 250 members. Even though the total number of participants was at most about 130, RERF staff members participating in the meeting numbered around 40.

Since last year, public interest in health effects of radiation has grown rapidly. Particularly concerning such issues as unsubstantiated low-dose radiation risk and hard-to-assess internal radiation exposure risk, information from a wide variety of sources is in general circulation, revealing a major problem in the area of risk communication. Furthermore, this field of research is still lacking in human resources. Consequently, it is hoped that the meeting provided the opportunity for as many investigators as possible to become interested in work on issues related to radiation epidemiology.

Lastly, I would like to express my heartfelt appreciation to Dr. Tomonori Hayashi, Assistant Chief of the Department of Radiobiology/Molecular Epidemiology, Dr. Ritsu Sakata, Associate

The 35th meeting of the Japanese Society of Cancer Epidemiology held at Aster Plaza in Hiroshima

Senior Scientist at the Department of Epidemiology, and the staff of the Secretariat and the Department of Epidemiology for their dedication to the success of the recent meeting. Dr. Hayashi handled lectures/posters relating to molecular epidemiology and provided advice relating to the program in a role akin to that of the meeting vice-president. Dr. Hayashi also made such practical arrangements as selection of the venue. Dr. Sakata worked on the handling of practical operations for the meeting. The staff of the Department of Epidemiology and Secretariat worked hard on preparations for the meeting and practical operations on the days of the meeting.

The Third Epidemiological Training Workshop for Biologists

Nori Nakamura, Chief Scientist

The third Epidemiological Training Workshop for Biologists, hosted by the Council of Radiation Effects Research Organizations, was held August 20–21, 2012, at the RERF Auditorium in Hiroshima. This year's workshop was attended by about 60 people (28 outside participants and 29 RERF staff). (The Council of Radiation Effects Research Organizations, consisting of Fukushima Medical University, Hirosaki University, Hiroshima University, the Institute for Environmental Sciences, Kyoto University, Nagasaki University, National Institute of Radiological Sciences, and RERF [in alphabetical order], was established to develop understanding among radiation research organizations and strengthen their alliance.)

Following opening remarks by Chairman Toshiteru Okubo, an explanatory session titled "Basics of radiobiology for non-biologists" (by Assistant Chief of Genetics Department Asao Noda and Chief Scientist Nori Nakamura) was introduced to the workshop this year on a trial basis, in response to requests from statisticians and epidemiologists. The hope was that the sharing of some degree of knowledge with biologists could enrich communication among the different disciplines. Also presented were lectures titled "From basics of epidemiology to A-bomb radiation effects" (by Dr. Ritsu Sakata, Research Scientist, Epidemiology Department) and "A-bomb survivor Life Span Study (LSS): descriptions of LSS Report 14" (by Chief of Epidemiology Department Kotaro Ozasa).

In the afternoon, such sessions as "Review of genetic effects of A-bomb radiation" (by Chief of Genetics Department Yoshiaki Kodama), "Descriptions of a paper by *Lancet* (2012) regarding radiation exposure from CT scans in childhood and subsequent risk of leukemia and brain tumors" (by Dr. Ozasa), "Review of risk for malignant tumors among the offspring of A-bomb survivors" (by Assistant Chief of Epidemiology Department Eric Grant), and "Problem presentation: whether or not risk to the fetus is higher than that to children" (by Dr. Hiromi Sugiyama, Research Scientist, Epidemiology Department, and Dr. Nakamura) were held, followed by a social gathering held outside RERF.

The workshop's second day featured such sessions as "Review of cardiovascular disease risk among A-bomb survivors" (by Dr. Ikuno Takahashi, Research Scientist, Clinical Studies and Epidemiology Departments), "Problem presentation: what effects of age at exposure mean" (by Dr. Nakamura), and "Discussion: whether decreased relative risk with increase in number of years after radiation exposure was caused by chance or necessity" (by Dr. Nakamura and Dr. Ohtsura Niwa, Pro-

Participants of the third epidemiological training workshop for biologists

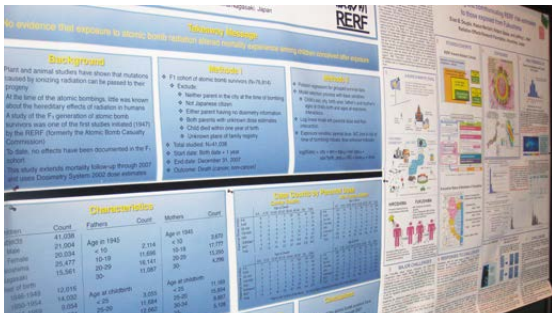
fessor Emeritus, Kyoto University). The workshop on that day concluded at noon.

After experiencing three such workshops held at RERF, I now understand the challenge of communication among such different fields of research. As mentioned above, the explanatory session regarding basics of radiobiology for non-radiobiologists was introduced to the workshop, but a portion of participants commented that the session was too difficult to totally understand. This issue points to the possibility that the workshop concept still has room for improvement. When preparing for the latest workshop, I grasped for the first time the significant difference between epidemiological research and animal experiments: the former aims at describing risk changes in small increments over time until completion of the research, whereas the latter work focuses for the most part only on lifetime risk (i.e., the percentage of tumor cases developing in a certain group). Furthermore, animal experiments sometimes do not involve lifelong observation (i.e., follow-up until natural death). Under such circumstances, it is impossible even to lay the groundwork for discussion about research into mechanisms behind carcinogenesis in parallel with the theme of epidemiological research. If an animal experiment were to try to carry out observations up to the point at which changes occur at the stage of cancer diagnosis, it would be necessary to target a large population (e.g., a population of at least 300 mice), making me feel that the current situation is unavoidable. If sufficient communication among different fields of research had taken place in the past, conduct of higher-quality animal experiments might have been possible, even though it is too late at this point in time, when the number of currently available animal experiment facilities is already limited.

The 58th Annual Meeting of the Radiation Research Society (September 30–October 3, 2012) in San Juan, Puerto Rico

Evan B. Douple, Associate Chief of Research

RERF was well represented at the 2012 meeting of the Radiation Research Society held in San Juan, Puerto Rico. Posters were presented by Evan B. Douple, Eric J. Grant (Assistant Chief, Epidemiology Department), Kazuo Neriishi (Part-time Professional, Vice Chairman's Office), and Ritsu Sakata (Associate Senior Scientist, Epidemiology Department). In addition, Harry M. Cullings (Chief, Statistics Department) was invited to participate in a symposium on Radiation-induced Occupational Cancer and Non-cancer Risks: Past, Present and Future Perspective. His presentation was titled "Incidence of leukemia, lymphoma, and multiple myeloma among the Japanese atomic-bomb survivors: 1950–2001" (based on the paper by Wan-Ling Hsu et al.). Dr. Douple was invited to present a topical review lecture on "Lessons learned from RERF and from Fukushima and other nuclear accidents for more effective communication of radiation risks."



Two of the three RERF posters presented at the Radiation Research Society meeting in Puerto Rico

Radiation Dose and Cataract Surgery Incidence in Atomic Bomb Survivors, 1986–2005*

Kazuo Neriishi

Part-time Professional, Vice Chariman's Office

*This article is based on the following publication:

Neriishi K, Nakashima E, Akahoshi M, Hida A, Grant EJ, Masunari N, Funamoto S, Minamoto A, Fujiwara S, Shore RE. Radiation dose and cataract surgery incidence in atomic bomb survivors, 1986–2005. *Radiology* 265:167–74, 2012 (doi:10.1148/radiol.12111947)

Introduction

Since the 1950s, the prevailing view had been that only relatively high doses of at least several gray (Gy) induce vision-impairing cataracts,[1] e.g., the International Commission on Radiological Protection (ICRP) judged that a brief exposure of at least 5 Gy was required or an even larger cumulative dose of protracted or fractionated radiation.[2,3] Several studies in the last couple of decades had found that radiation doses under 1 Gy were associated with primarily low-grade opacities that have little effect on visual acuity, but virtually no data were available on radiation and clinically significant cataracts. In 2007 we published data on radiation dose and the prevalence of cataract surgery in a subset of the Adult Health Study (AHS) cohort, showing a dose response with an estimated 39% excess relative risk at 1 Gy and no clear evidence for a dose threshold, albeit the data also were compatible with a dose threshold of up to 0.8 Gy.[4] That study played a large role in the recent revision of the ICRP guidelines indicating that eye lens doses should be limited to <0.5 Gy, a 10-fold reduction in the dose limit.[5]

However, cross-sectional prevalence studies have certain methodological limitations that may produce biased risk estimates; furthermore the sample size of the prevalence study was fairly small, so we believed that a longitudinal incidence study of cataract surgery was needed. That led to the present study which compiled the frequency of incident cataract surgery (i.e., an individual's first cataract surgery) among the 6,066 eligible participants in the AHS during the time period 1986–2005.

The three main objectives of the current study were: (a) to quantify the degree of cataract surgery risk from radiation, adjusting for other cataract risk variables that might be confounders; (b) to determine whether the dose-response association is approximately linear or has upward curvature; and (c) to estimate the dose-effect threshold level. The current study examines the incidence of clinically important cataracts in relation to lens doses between 0 and approximately 3 Gy to address risks at relatively low brief radiation doses.

Materials and Methods

Materials

Since 1958, the AHS has conducted biennial clinical health examinations of individuals exposed to the atomic bomb (A-bomb).[6] Beginning in 1986, cataract surgery, as confirmed by using ophthalmoscopic examination, was systematically recorded in the medical charts. For the current study, chart reviews of all study subjects were conducted by experienced physicians to assure accurate coding of cataracts. Incident cases of surgically removed cataracts (i.e., their first cataract surgery) among AHS subjects were identified during 1986 through 2005. For dose-response analyses, we used the eye radiation absorbed dose in Gy, which is the sum of the gamma dose plus 10 times the neutron dose based on the current Dosimetry System 2002[7] and adjusted for dose measurement error.[8] Sixteen lens opacity risk factors were identified from the literature[9–12] for which questionnaire or observational information was available, including the following: education; marital status; history of smoking; body mass index; systolic and diastolic blood pressure; platelet count; lactic acid dehydrogenase level; uric acid level; γ-glutamyltransferase level; history of diabetes mellitus, hypercholesterolemia, hypertension, angina pectoris, or myocardial infarction; and corticosteroid medication use. Between 1986 and 2005, 8,055 individuals visited the AHS clinics more than once, so that new incident cases could be identified (at the initial visit during that period, prevalent cases were identified, while at subsequent visits, new, incident cases of cataract surgery were identified), but some were inappropriate for inclusion: 1,861 individuals who were prenatally exposed or whose radiation doses were unknown, 122 individuals who underwent cataract surgery before

January 1986, and six individuals in whom the date of surgery was unknown. That left 6,066 eligible individuals (without a prior cataract surgery) who were considered at risk beginning at their first AHS clinic attendance date after January 1, 1986, until cataract surgery was performed, the last date of attendance at the AHS clinic, or December 31, 2005, whichever occurred first.

Statistical methods

The first phase of the analysis consisted of an examination of the 16 identified cataract risk factors to determine which were potential confounder variables by using Cox regression.[13] The basic variables for the risk factor analysis also included the demographic variables of city, sex, age at exposure, and attained age, plus eye radiation dose. These were analyzed in a multivariate model adjusted simultaneously for all the other risk factors. The analyses suggested that the only risk-factor variable that might be a confounder was diabetes mellitus, so it was adjusted for in the radiation-risk models.

In the second phase to assess radiation risk, excess incidence was modeled as both excess relative risk (ERR) at 1 Gy and excess absolute risk (EAR) expressed per 10,000 persons per year at 1 Gy by using the Amfit program in the Epicure statistical package[14] to perform Poisson regression of grouped data. Poisson regression allows the risk to be partitioned into background risk, dose effects, and dose-effect modifiers. For the analysis, the person-year data were simultaneously stratified according to city, sex, diabetes mellitus, age at exposure, attained age, time since exposure, and eye radiation dose (≤0.005, 0.005–, 0.03–, 0.1–, 0.2–, 0.4–, 0.6–, 0.8–, 1.0–, 2.0–3.0, >3.0 Gy). Diabetes mellitus status was coded as positive for a diabetes diagnosis prior to lens surgery or at any time during an individual's follow-up if there was no surgery. Both ERR and EAR models were fitted, including city, sex, diabetes mellitus, age at exposure, and either attained age or time since exposure (TSE) to model background risk and as potential radiation dose-effect modifiers. Because TSE is a more natural way of describing radiation risk than is attained age, unless the attained-age model fits the data appreciably better than the TSE model, the TSE model was chosen. In both the ERR and EAR models, the eye dose term was modeled both as linear and linear-quadratic to better assess low-dose risk levels. Both the two-sided significance tests and 95% confidence intervals (CI) were based on likelihood ratio tests applied to the profile likelihood.[15] The magnitude of the dose-response threshold level was estimated on the basis of the optimal model from the radiation-risk analysis.

Results

Population description

There were 1,028 persons with initial cataract surgery between 1986 and 2005 among the 6,066 study subjects who contributed 84,209 person-years. Table 1 shows the numbers of cataract surgery cases and person-years according to eye radiation dose, sex, city, and age at exposure. The cumulative incidence of cataract surgery was similar in the two cities, but the crude cumulative incidence of cataract was higher in females (18.5%, 745 of 4,035) than in males (13.9%, 283 of 2,031). The mean age at exposure was 20.4 years (range, 0–54 years). For both sexes, the mean age at cataract extraction was 74.4 years, and the range was 49–95 years. The mean lens dose across all study subjects was 0.50 Gy (range, 0.0–5.14 Gy).

Table 1. Person-years (PY), cataract surgery cases, and crude incidence rates per 10,000 PY by DS02 eye dose categories, city, gender, and age at exposure

	Person-years (PY)	Cases	Rate per 10,000 PY
Gender			
Male	28,097	283	101
Female	56,112	745	133
City			
Hiroshima	53,724	646	120
Nagasaki	30,485	382	125
Age at exposure (y)			
<10	16,267	66	41
10–	37,404	412	110
20–	19,458	350	180
≥30	11,081	200	180
Dose (Gy)			
<0.005	35,821	386	108
0.005–	19,101	234	123
0.4–	14,345	182	127
1.0–	10,328	148	143
2.0–	2,764	43	156
≥3.0	1,849	35	189
Total	84,209	1,028	122

Risk factor analysis for potential confounding variables

Table 2 shows the distribution of cataract risk factors and the Cox hazard ratios (HRs) for dose, the basic demographic adjustment variables, and the most relevant covariates. The HRs are shown while simultaneously adjusting for all 16 potential risk factors by using multivariate analysis. Significant risk variables in the multivariate analysis were diabetes mellitus, angina pectoris, no college education, and a high body mass index. However, adjustment for all the covariates simultaneously had almost no effect on the radiation risk, indicating they were not material confounders. Specifi-

Table 2. Cox regression hazard ratios (HR) and 95% confidence intervals (CI) for demographic factors, radiation dose, and cataract surgery risk factors

Covariate	Cataract cases/Total subjects	Adjusted analyses†	
		HR	CI
City			
Hiroshima	646/3,985	1	–
Nagasaki	382/2,081	1.19	1.03, 1.36
Gender			
Male	283/2,031	1	–
Female	745/4,035	1.16	0.96, 1.41
Age at exposure (y)			
0–<10	66/ 967	1‡	–
10–<20	412/2,376	2.68	2.08, 3.52
20–<30	350/1,459	4.99	3.81, 6.63
≥30	200/1,264	7.64	5.67, 10.4
DS02 eye dose (Gy)			
0–<0.005	386/2,530	1‡	–
0.005–<0.4	234/1,402	1.10	0.93, 1.30
0.4–<1.0	182/1,027	1.15	0.96, 1.37
1.0–<2.0	148/ 750	1.37	1.13, 1.65
2.0–<3.0	43/ 212	1.92	1.38, 2.60
≥3.0	35/ 145	2.19	1.52, 3.06
Education			
Junior high§	434/2,646	1	–
High school	529/2,854	1.08	0.94, 1.23
College	65/ 566	0.76	0.57, 0.98
Smoking			
Never§	686/3,774	1	–
Ex-smoker	173/ 956	1.20	0.98, 1.45
Current	169/1,336	0.87	0.71, 1.07
Body mass index (kg/m^2)			
<20§	244/1,624	1‡	–
20–<25	554/3,190	0.92	0.79, 1.08
25–<30	210/1,123	0.89	0.73, 1.09
≥30	20/ 129	0.63	0.38, 0.99
Diabetes mellitus			
No	891/5,478	1	–
Yes	137/ 588	1.85	1.53, 2.22
Hypercholesterolemia			
No§	949/5,713	1	–
Yes	79/ 353	1.07	0.84, 1.34
Hypertension			
No	572/3,484	1	–
Yes	456/2,582	1.05	0.90, 1.23
Angina pectoris			
No	960/5,762	1	–
Yes	68/ 304	1.31	1.01, 1.66
Myocardial infarction			
No	1,020/6,002	1	–
Yes	8/ 64	0.87	0.40, 1.64
Oral/Injected corticosteroids			
No§	1,003/5,944	1	–
Yes	25/ 122	1.12	0.73, 1.63

† Analyses including adjustment for the basic variables (city, gender, age at exposure, and radiation dose) plus all 16 risk-factor variables
‡ P for trend < 0.05
§ Includes unknown or missing data (for <10% of the total subjects)

cally, the dose response using Cox regression, including dose as a continuous variable and only the basic demographic variables (HR, 1.28 at 1 Gy; 95% CI: 1.19, 1.37), was nearly the same as when all 16 potential confounders also were included (HR, 1.26 at 1 Gy; 95% CI: 1.17, 1.35), indicating the absence of confounding effects. Nevertheless, because diabetes mellitus was a strong risk factor for cataract, we included it in further Poisson regression analyses.

Radiation risk analysis

For the Poisson regression, the best sets of background rates (which included some interactions among city, sex, and age) and effect-modification terms were found. For the ERR models, the TSE model fit the data slightly better than the attained-age model, so the TSE model was used. However, for the EAR models, the attained-age model provided a better fit than the TSE model, so it was used. In the following, risk estimates are presented for an attained age of 70 years after exposure at age 20 years, unless otherwise noted.

ERR models—After optimizing the background model, the simplest TSE ERR model with no dose-effect modifiers yielded a linear dose-response ERR estimate of 0.32 (95% CI: 0.20, 0.47) at 1 Gy. When a quadratic dose-squared term was added to the model, its effect was positive, suggesting slight upward curvature, but the improvement in fit was not significant (P = 0.34), so it was not pursued further. Evaluation of potential effect modifiers showed that city (P = 0.05), sex (P = 0.03), age at exposure (P = 0.006), and TSE (P < 0.001), but not diabetes mellitus, modified the radiation effect, with Nagasaki, male sex, younger age at exposure, and shorter TSE having greater radiation ERRs. With the effect modifiers of city, sex, age at exposure, and TSE, the ERR estimate was calculated as follows:

$$0.77 \cdot d \cdot \exp(20.88 \cdot c - 0.89 \cdot s - 0.66 \cdot e - 1.59 \cdot TSE),$$

where d is eye radiation dose, c is city, s is sex, and e is (years of age at exposure – 20)/10, and TSE is (years since exposure – 50)/10.

With use of this model, the sex-averaged ERR for Hiroshima for a 70-year-old individual exposed at age 20 years (i.e., 50 years after exposure) was 0.32 (95% CI: 0.09, 0.53; P < 0.001) (Figure 1). The estimated number of excess cases caused by radiation was 109. Averaged across city, the estimated ERR was 0.49 for males and 0.20 for females. When averaged across city and sex, the estimated ERR was greater at younger ages at exposure; estimates for 50 years after exposure were 0.61, 0.32, and 0.15 for exposure at ages 10, 20, and 30 years, respectively. The negative coeffi-

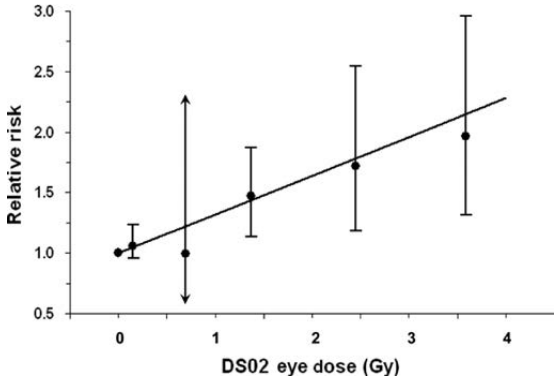


Figure 1. Radiation dose response for the relative risk of cataract surgery for 20 years of age at exposure and attained age of 70 years, and averaged across gender and city. The excess relative risk per Gy was 32% (95% CI: 9%, 53%) (P < 0.001).

cient shown for the TSE modifier in the above equation indicates that the ERR diminished at longer times since radiation exposure.

EAR models—With the best background model, the simplest EAR model with no dose-effect modifiers yielded a linear dose-response EAR estimate of 19.0 (95% CI: 11.7, 27.2) excess cases per 10,000 person-years at 1 Gy. When a quadratic term was added to the model, the effect was positive but the improvement in the fit was not significant (P = 0.14). Evaluation of potential effect modifiers showed that city (P = 0.10), sex (P = 0.31), age at exposure (P = 0.31), and diabetes mellitus (P = 0.44) effects were not significant. Only a positive log attained age effect (P < 0.01) modified the radiation effect. The final EAR model was as follows: $33.2 \cdot d \cdot \exp(3.76 \cdot \log \text{age})$, where log age is log attained age.

Thus, the EAR was 33.2 (95% CI: 22.1, 45.2; P < 0.001) excess cases per 10,000 person-years at 1 Gy, modeled at age 70 years after exposure at age 20 years (Figure 2). On the basis of this model, the estimated number of excess cases caused by radiation was 117. The estimated EAR (averaged across city, sex, and age at exposure) increased with attained age: The EAR was 19 (95% CI: 12, 26) at age 60 years, 33 (95% CI: 22, 45) at age 70 years, and 55 (95% CI: 31, 83) at age 80 years, but it was not significantly affected by age at exposure (P = 0.31).

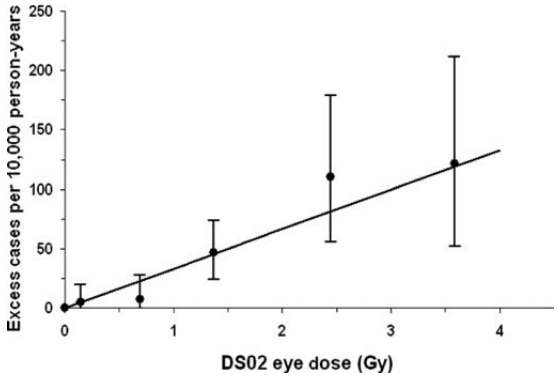


Figure 2. Dose response: excess absolute risk (EAR) per 10,000 persons per year, modeled for 20 years of age at exposure and attained age of 70 years, averaged across gender and city. The excess cases per 10,000 persons per year per Gy were 33 (95% CI: 22, 45) (P < 0.001).

Threshold level search—With the best models shown above, we searched for a threshold dose effect by using a profile likelihood search. The threshold-dose point estimates were similar for the two models: 0.50 Gy (95% CI: 0.10 Gy, 0.95 Gy) for the ERR model and 0.45 Gy (95% CI: 0.10 Gy, 1.05 Gy) for the EAR model.

Discussion

This study provides quantitative evidence for risk of vision-impairing cataracts at lens doses less than 1 Gy. The dose response was nearly linear, implying there may be risk at fairly low doses. The best estimate was a 32% excess in the relative risk at 1 Gy for a 70-year-old individual who received radiation exposure at age 20 years. The risk was highest for those who were young at exposure, suggesting that children are especially sensitive to cataract induction by means of radiation. A formal dose-threshold level analysis provided a best estimate of a threshold level at about one-half of a gray but indicated that the threshold level may be as low as 0.1 Gy and is unlikely to exceed 1.0 Gy. As such, these data strengthen the foundation for the recent ICRP guidelines in which the threshold level for absorbed dose to the lens has been reduced by a factor of 10 to 0.5 Gy.[5]

A substantial number of screening studies,[16–22] including several of medical radiation personnel,[23–26] have reported that doses of low-linear energy transfer radiation less than 1 Gy are associated with posterior subcapsular and cortical opacities, but they were primarily low-grade opacities that have little effect on visual acuity. Further details are given in two reviews.[27,28] Researchers in two previous studies[29,30] have reported on clinically important cataracts, but one was based on alpha irradiation with uncertain dosimetry,[29,30] and the other did not show a significant association but, because of the very low dose distribution, had limited statistical power.[9] Thus, the present study provides more convincing evidence than that in previous studies about clinically significant cataracts caused by radiation in the 0–1 Gy dose range, given that it reflects cataract-surgery incidence during a 20-year period in a large cohort of whom more than 1,000 individuals underwent cataract surgery, and 82% of the cohort received doses less than 1 Gy.

Past estimates of threshold doses have been based on prevalence analyses in A-bomb survi-

vors[4,22,31] and Chernobyl clean-up workers[18]; all except one[31] suggested a low-dose threshold level.

This study had a number of strengths. It characterized the radiation risk for cataract surgery incidence in a well-defined cohort with a wide range of reasonably accurate dose estimates and a high participation rate for up to 60 years after the bombings. Those who performed the medical examinations for confirmation of cataract were blinded to the radiation dose so as not to bias the assessment. Furthermore, bias from differential care seeking is unlikely because there were no economic incentives for some subgroups to get more health care than others, as health care is free and readily available for all study subjects.

The study also had certain limitations. We did not account for possible temporal changes in smoking habits, alcohol consumption, or obesity (body mass index) during the study period. Information on individual sunlight exposure was not available, although it is known that the cohort contained few individuals who had marked occupational sunlight exposure, and there is no apparent reason why sunlight exposure should be correlated with radiation dose. There may have been losses to follow-up or survival biases in the cohort before 1986 (which was 41 years after the bombings). However, losses to follow-up (participant attrition) have been independent of radiation dose in the AHS, and the modest dose-related differences in survival as a result of the radiation-cancer association are unlikely to be related also to cataract outcomes. Cataract surgery is an imperfect surrogate for a vision-impairing cataract because surgery may depend on health status, age, visual acuity in the other eye, and other factors that limit the sensitivity in ascertaining vision-limiting cataracts,[32] but there is no reason to think that the sensitivity varied by radiation dose. Because the study was based on a brief, single radiation exposure, the generalization of the risk estimates to groups exposed to protracted or highly fractionated radiation is uncertain.

In conclusion, a 32% (95% CI: 9%, 53%) excess was found at 1 Gy in the relative risk for incident cataract surgery, an excess amounting to 33 extra cases per 10,000 persons per year per gray. The near-linear dose response suggests there may be radiation risk for clinically important cataracts at relatively low doses, and the data are compatible with a dose-response threshold level between about 0.1 and 1 Gy but not with threshold values above 1 Gy. Finding a near-linear dose response and an estimated-dose threshold level of approximately 0.5 Gy for clinically important cataracts among A-bomb survivors significantly strengthens the scientific foundation for the recent ICRP statement[5] that considers the threshold dose for the lens of the eye to be 0.5 Gy rather than a much higher value.

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Long-term Trends of Thyroid Cancer Risk among Japanese Atomic-bomb Survivors: 60 Years after Exposure*

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Furukawa K, Preston DL, Funamoto S, Yonehara S, Ito M, Tokuoka S, Sugiyama H, Soda M, Ozasa K, Mabuchi K. Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. *Int J Cancer* 2012 (August 16) [Epub ahead of print] (doi:10.1002/ijc.27749)

Findings of This Study

Among the A-bomb survivors exposed to radiation before reaching adulthood (before age 20), risk of thyroid cancer incidence tended to increase with radiation dose. Although excess risk (relative increase in incidence based on comparison with the non-exposed) from childhood exposure decreases with attained age, the risk persists more

Table. Observed and fitted cases of thyroid cancer incidence in the LSS (1958–2005) by categories of dose and other variables

	Age at exposure < 20 years							Age at exposure >= 20 years						
				Fitted values							Fitted values			
	n	Case	Rate[a]	Back-ground	Fitted excess	AF[b] (%)	95% CI	n	Case	Rate[a]	Back-ground	Fitted excess	AF[b] (%)	95% CI
Total														
	45,738	191	12.2	153.5	41.1	36*	(22, 46)	59,663	180	12.5	173.2	3.3	4*	(1, 17)
Sex														
Male	21,571	40	5.6	33.7	5.6	14	(0, 27)	21,319	21	5.0	21.6	0.2	1	(0, 6)
Female	24,167	151	17.5	119.7	35.5	23	(13, 32)	38,344	159	15.5	151.6	3.1	2	(0, 9)
Weighted thyroid dose (Gy)														
NIC	10,867	33	8.6	26.6	0.0	0	(0, 0)	14,377	25	6.9	31.4	0.0	0	(0, 0)
0–0.005	15,243	45	8.8	53.9	0.1	0	(0, 0)	19,071	61	13.4	57.7	0.0	0	(0, 0)
0.005–0.1	12,143	37	8.8	39.6	2.7	6	(3, 9)	15,485	50	13.5	46.3	0.2	0	(0, 2)
0.1–0.25	2,981	20	19.1	10.9	3.8	26	(14, 35)	4,308	17	16.4	14.2	0.3	2	(0, 11)
0.25–0.5	1,798	15	24.0	7.5	5.3	41	(25, 53)	2,695	11	17.1	9.2	0.4	4	(1, 22)
0.5–1	1,405	15	31.8	7.6	9.0	54	(38, 66)	2,111	8	16.0	8.0	0.7	9	(2, 35)
1+	1,301	26	63.5	7.3	20.1	73	(59, 83)	1,616	8	21.8	6.4	1.7	21	(6, 59)
Attained age (year)														
–39		38	5.9	24.9	13.4	35	(13, 52)		3	7.8	2.6	0.3	9	(2, 31)
40–49		34	10.2	26.3	8.6	25	(14, 33)		15	9.2	13.2	0.6	5	(1, 18)
50–59		53	16.8	41.3	10.4	20	(10, 28)		29	9.5	29.6	0.7	2	(0, 12)
60–69		45	21.0	42.2	6.9	14	(6, 22)		44	11.2	45.0	0.7	2	(0, 8)
70–		21	30.3	18.8	1.8	9	(3, 17)		89	16.4	82.7	0.9	1	(0, 6)
Calendar year														
1958–1965	45,738[c]	22	7.1	11.2	5.7	34	(8, 58)	59,663[c]	45	10.8	41.9	0.7	2	(0, 10)
1966–1975	45,042	17	4.8	17.0	6.6	28	(12, 42)	50,421	40	9.5	40.7	0.7	2	(0, 9)
1976–1985	43,890	31	9.3	26.0	7.9	23	(13, 32)	38,379	30	9.9	36.1	0.7	2	(0, 8)
1986–1995	41,971	57	18.4	40.0	9.6	19	(10, 27)	26,396	44	22.6	31.1	0.7	2	(0, 8)
1996–2005	38,181	64	23.6	59.3	11.1	16	(6, 24)	15,416	21	20.3	23.4	0.5	2	(0, 8)

a: Cases per 100,000 person-years (PY)
b: Attributable faction (*among people with dose greater than 0.005 Gy weighted thyroid dose)
c: The number of subjects at risk at the beginning of the period
NIC: Subjects who were not in the cities at the time of bombings

than 50 years after the atomic bombings. On the other hand, no clear effect on thyroid cancer was observed from radiation exposure occurring in adulthood (at or after age 20).

Explanation

Thyroid cancer, while not a frequent cancer, has a relatively strong association with radiation, and it was a type of solid cancer for which association with radiation was identified early on (10-plus years after the atomic bombings) in research involving the A-bomb survivors. Multiple epidemiological and other studies have reported that the thyroid is highly susceptible to the effects of radiation exposure before adulthood in particular, but not much has been elucidated in terms of whether there are any long-term exposure effects or effects from exposure after reaching adulthood. In this study of approximately 100,000 members of the 120,000-subject Life Span Study (LSS) cohort, the authors analyzed association between thyroid cancer incidence and exposure dose up to 60 years after the atomic bombings using the latest cancer incidence data including detailed pathological diagnoses.

1. Purpose of study: To examine long-term temporal trends and age-at-exposure variations in radiation-induced risk of thyroid cancer.

2. Based on the cancer incidence data including detailed pathological diagnoses: 371 thyroid cancer cases (first primary) were clinically and microscopically confirmed among 105,401 cohort members for the period from 1958 through 2005 (Table). Poisson regression models were used for analyzing association between thyroid cancer incidence and radiation dose, age, sex, and other factors.

3. Results of the study: For exposure to 1 Gy of radiation at age 10, it was estimated that thyroid cancer incidence at age 60 would increase by 128% (95% confidence interval [CI]: 60–270%) compared with that of the non-exposed, or an increase of 2.28 times (Figure 1). Radiation-associated excess risk based on the same attained age decreased sharply with increasing age at exposure, and there was no clear evidence of increased thyroid cancer rates for those exposed at or after age 20 (Figure 2). About 36% of the 113 thyroid cancer cases among the LSS cohort exposed to radiation of at least 5 mGy before age 20 were estimated to be attributable to radiation exposure (Table). While excess risk of thyroid cancer associated with childhood exposure has decreased with increasing attained age, excess risk persists even after more than 50 years since exposure.

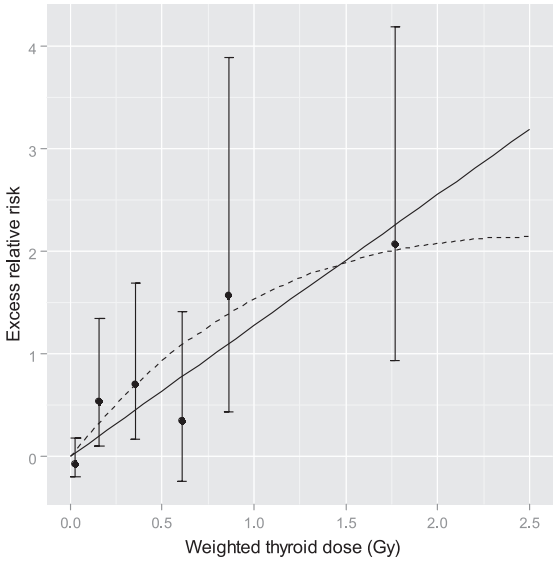

Figure 1. Fitted dose response functions for thyroid cancer incidence in the LSS cohort. The solid line is the fitted linear excess relative risk (ERR) dose response, and the dashed curve is the fitted ERR based on linear-exponential dose response model. The points are non-parametric estimates of the ERR in dose categories with 95% CIs. The line and points are all gender-averaged estimates at age 60 after exposure at age 10.

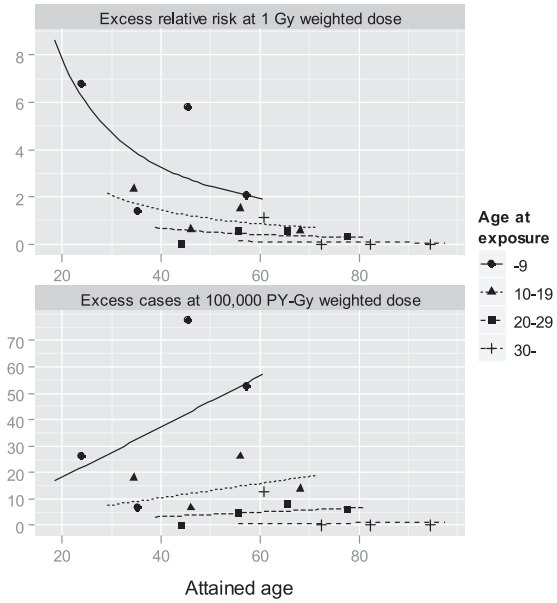

Figure 2. Fitted temporal patterns and age-at-exposure variation in the radiation-associated risk for thyroid cancer in the LSS cohort. The upper panel presents ERR at 1 Gy and the lower panel the fitted excess absolute rate at 100,000 person-years-Gy, with attained age for ages at exposure of 5 ("0–9" for categorical estimates), 15 ("10–19"), 25 ("20–29") and 41 ("30–") years. All curves and points are gender-averaged estimates.

Farewell Service and Memorial Gathering Held for the Late Dr. Itsuzo Shigematsu

Kazunori Kodama, Chief Scientist
Yutaka Ogasawara, Assistant Chief of Secretariat
Ayako Ishibe, Directors' Office

Dr. Itsuzo Shigematsu, who had served as RERF Emeritus Consultant after a distinguished term of 16 years as RERF Chairman, passed away on February 6, 2012. The following is our report on his farewell service and memorial gathering held in Tokyo and Hiroshima, respectively.

Farewell Service for Dr. Itsuzo Shigematsu

The farewell service for the late Dr. Itsuzo Shigematsu was held at the Gakushi Kaikan in Tokyo on April 22, 2012. The service was organized by RERF Chairman Toshiteru Okubo, former RERF Vice Chairman Senjun Taira, and five other persons, and its representative working committee members included one of us (KK) and Dr. Hiroshi Yanagawa (professor emeritus of Jichi Medical University, former Saitama Prefectural University President), who was a favorite pupil of Dr. Shigematsu's.

Family members of the deceased were in attendance, including Dr. Shigematsu's wife Mrs. Yoshie Shigematsu, eldest son Mr. Ken Shigematsu and his wife, daughter Mrs. Eiko Sato, and three grandchildren. The service was a truly stately occasion, with attendance of a total of 232 guests that packed the venue including Dr. Senya Toyama, Director-General of Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW), Dr. Shigenobu Nagataki, former RERF Chairman, those working in the fields of epidemiology and public health, and many students of the deceased.

With Dr. Yanagawa presiding over the service, there was a silent prayer offered to the soul of the deceased, followed by representative organizer's greetings by Dr. Okubo, and words by which to remember the deceased delivered by Dr. Tadao Shimao (Chairman of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors), Dr. Nagataki, and six more guests.

At the service venue, an exhibit of posters featured many memorable photographs of Dr. Shigematsu during childhood, as a student, in the military, when he was with the Japanese Institute of Public Health, at Kanazawa University, and at RERF, all of which were prepared through the determined efforts of volunteers from RERF, Jichi Medical University, and Saitama Prefectural University. Moreover, the venue exhibited numerous items related to Dr. Shigematsu including awards/medals and commendations, and a model of the light cruiser *Kuma*, on which Dr. Shigematsu served when he was in the Japanese Navy. While viewing the memorial items, the attendees reminisced about their shared past with Dr. Shigematsu.

Many messages arrived from overseas sent by those mourning Dr. Shigematsu's passing, including Director Patricia R. Worthington, Office of Health and Safety, Office of Health, Safety and Security, Department of Energy, former RERF Chairman Burton G. Bennett, former RERF Vice Chairman J.W. Thiessen, WHO Emeritus Director-General Hiroshi Nakajima, Professor Emeritus K. Sankaranarayanan of Leiden University, who was Dr. Shigematsu's epidemiologist friend from long ago, and Dr. Warren K. Sinclair, U.S. Chairman of the Senior Review Group for DS02.

Finally, the eldest son Mr. Ken Shigematsu spoke on behalf of the bereaved family, and the two-hour service came to an end with Dr. Taira's closing address. We later received positive feedback from the attendees that it had been a memorable and meaningful occasion.

A collection of essays contributed by more than 100 persons titled "To Dr. Itsuzo Shigematsu with Gratitude" was presented to the attendees as a remembrance.

At the farewell service for Dr. Itsuzo Shigematsu (Tokyo)

Memorial Gathering for Dr. Itsuzo Shigematsu

The memorial gathering for Dr. Itsuzo Shigematsu was held at Hiroshima City Bunka Koryu Kaikan (former Kosei-Nenkin Kaikan) on June 30, 2012. The event was organized by RERF Chairman Toshiteru Okubo, Dr. Nanao Kamada, Dr. Kozo Sanada, and Dr. Hiroo Dohy—the present and former presidents of the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE)—and Mr. Toraji Miyagawa, President, ABCC-RERF Hiroshima OB-Kai (Retirees Club). I (KK) served as the representative working committee member.

There were a total of 103 participants at the gathering: seven bereaved family members from Tokyo including Dr. Shigematsu's wife Yoshie, and relevant individuals in the local area from Hiroshima Prefecture and City governments, Hiroshima University, Hiroshima Prefectural and City Medical Associations, the local news media, A-bomb survivors, former and present employees at ABCC-RERF, and individuals from Nagasaki.

Ms. Reiko Horimukai served as emcee of the gathering. Following a moment of silence, Dr. Okubo delivered representative organizer's greetings, and then former RERF Vice Chairman William J. Schull, who came to Hiroshima all the way from Houston, spoke of his memories of Dr. Shigematsu.

The gathering in Hiroshima had several unique characteristics: to note among them was a piano recital by Dr. Shigematsu's granddaughter, Hanako Shigematsu, who is an established pianist. Hanako performed two poignant pieces, interspersed with remembrances of her late grandfather. The gathering also included a slideshow titled "Dr. Shigematsu, Hiroshima, and us," during which we talked about Dr. Shigematsu's 16 years in Hiroshima based on a presentation mainly of slides I (KK) had prepared. In addition, we showed a video recording of some of Dr. Shigematsu's lectures and interviews. We believe that all attendees were able to share with each other their many valuable memories of Dr. Shigematsu. Posters and items exhibited at the farewell service in Tokyo were also used at this memorial gathering in Hiroshima.

Finally, Mr. Ken Shigematsu then spoke on behalf of the bereaved family, and the memorial gathering came to an end with Dr. Kamada's closing address.

The planning and implementation of the gathering were handled by RERF volunteers, all of whom provided dedicated service. We would like to take this opportunity to thank all RERF employees, including those not directly involved in the relevant work, for their help in putting on the event.

We would like to close this report by once again expressing our deepest condolences on the passing of Dr. Shigematsu.

At the memorial gathering for Dr. Itsuzo Shigematsu (Hiroshima). Mr. Ken Shigematsu (far left) offering words of gratitude on the bereaved family's behalf.

In memory of Dr. Shoji Tokuoka

Kazunori Kodama, Chief Scientist

Dr. Shoji Tokuoka, who had dedicated himself for so long to the development of pathological research at RERF, passed away on September 29, 2012. He was 85 years of age. I would like to express my heartfelt appreciation for all of his contributions over so many years and extend my deepest condolences to his family.

Dr. Tokuoka was born in 1927, graduated from Hiroshima Medical College in 1952, and started his career in the field of pathology. He worked as a resident at the Institute of Pathology, University of Tennessee School of Medicine, Memphis, Tennessee, and at the Department of Pathology, the University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas, for a total of three years. He then served as an associate professor in pathology at Hiroshima University Faculty of Medicine, and as a professor in pathology, Kagoshima University Faculty of Medicine, before assuming the post of pathology professor, Hiroshima University Faculty of Medicine. Starting in 1986, he served as dean of the Hiroshima University Faculty of Medicine for two years.

Dr. Tokuoka's involvement in research on late effects of A-bomb radiation began in 1959, when he was appointed to serve as a contract pathologist at the Atomic Bomb Casualty Commission (ABCC). After ABCC's reorganization into RERF, he served as an expert advisor and a consultant to the Department of Pathology (later Department of Epidemiologic Pathology) starting in 1976 and 1982, respectively, providing research guidance to RERF researchers. Starting in 1986, he concurrently served as a consultant to the Department of Radiobiology. After his retirement from Hiroshima University, he assumed the newly created post of senior consulting scientist at RERF and engaged in research himself as an RERF consultant from 1994 until his death in 2012. He remained active as a researcher until that time.

Dr. Shoji Tokuoka in 2009

At RERF, Dr. Tokuoka focused on site-specific cancer research into association between A-bomb radiation and cancer risks based on extraordinarily accurate diagnoses made by utilizing local cancer registries and tissue registries, the latter of which are based on pathologist reports and both of which were implemented in Hiroshima and Nagasaki earlier than most of other registries in Japan. This research has been the centerpiece of the collaborative studies between RERF and the U.S. National Cancer Institute's Center for Cancer Research, leading to numerous papers on cancers of the liver, salivary gland, skin, thyroid, ovary, breast, lung, brain tumor, and lymphoma. This research has been taken over by researchers mentored by Dr. Tokuoka and successfully continues to date.

Dr. Tokuoka devoted his life to pathological research as just described, and I understand that his grandson has decided to tread in his grandfather's footsteps by launching his career in the same field of pathology. I am sure that Dr. Tokuoka would feel reassured and pleased.

In conclusion, I would like again to express my heartfelt appreciation for Dr. Tokuoka's contributions to the progress of RERF's research over so many years. May his soul rest in peace.

Public Relations Activities at RERF

Takanobu Teramoto, Executive Director

RERF conducts its public relations activities with the aim of enhancing the transparency and promoting the positive contributions to society of the foundation's scientific research. With the drastic increase in inquiries for radiation-risk information in the wake of the Fukushima nuclear crisis in March 2011, we are placing ever more emphasis on communicating accurate information on radiation risk.

Among the different means for public relations, the internet is crucial for the foundation's worldwide information dissemination as it aims to contribute to improving human health the world over. The RERF website is presented in both English and Japanese to provide information on radiation risk and RERF's recent papers and events. Moreover, data on the Life Span Study (LSS) and RERF's other major research projects are available on the website for outside researchers to download for use in their own research.

Immediately following the Fukushima nuclear crisis, RERF developed a special website in English and Japanese to start providing information most relevant to radiation risk and exposure. At the peak on March 15, 2011, the number of daily access registered to RERF's website was approximately 2 million hits (increase of about 50 times the number before the crisis) and 30,000 visitors (an increase of more than 20 times), respectively. A considerable number of questions regarding radiation risk reach RERF via its website, and with help from the research staff, RERF has responded to each inquiry.

An important part of our public relations activities is introducing the foundation's research to the public, including the A-bomb survivors in Hiroshima and Nagasaki, to gain their support and understanding of our work. RERF's Open House events are held at both the Hiroshima and Nagasaki Laboratories every August and represent the foundation's largest public outreach effort planned and carried out by the foundation's employees. The events are held over two days in each of the cities on the A-bombing anniversaries (August 6 for Hiroshima and August 9 for Nagasaki) and the day preceding each date. At such times, RERF welcomes many visitors from throughout Japan and from abroad. The Open House features exhibits introducing RERF's research programs, lectures, and scientific experiments, with the foundation's officials, research scientists, and general employees alike available for offering explanations to the visitors. Attracting about 1,300 visitors in Hiroshima and Nagasaki combined, this year's Open House events included a special exhibit on low-dose exposure in hopes of widely conveying to as many people as possible accurate information regarding radiation risk. Aspiring to remain a friendly research organization, RERF officials and employees make an effort to warmly greet the Open House visitors, from whom we have received positive feedback. Visitors are welcome to tour RERF's facilities at other occasions besides the Open House events, and during the school excursion seasons of spring and fall in particular, we welcome many young student visitors.

Executive Director Takanobu Teramoto briefing Open House visitors in Hiroshima

Students on a school excursion touring the RERF facilities in Hiroshima

RERF started holding its public lecture series in 2010. We hold such lectures in conference halls at the Peace Memorial Parks in Hiroshima and Nagasaki. The second public lectures, held in 2011–2012, aimed at communicating with the public about accurate information about radiation risk and featured two talks titled "Thinking about low-dose radiation exposure" and "Methods for radiation dose assessment."

Since the number of interviews and stories requested by the mass media drastically increased following the Fukushima nuclear crisis, in 2011 we initiated a seminar specifically designed for the journalists and reporters. Our focus for the media seminar is again to communicate accurate information on radiation risk. In addition, we have held press conferences and sent out press releases when major events are held and papers are released.

RERF will continue making efforts to conduct its public relations activities systematically and deliberately for the purpose of improving transparency of its research and publicizing its research achievements.

Recent Publications

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