放影研 RERF

update

Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan

Volume 21, Issue 2, 2010

Radiation Effects Research Foundation

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

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Contributions to 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 reflect RERF policies or positions.*

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From the Editors

Welcome back!

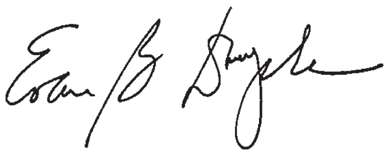
The beauty of the kōyō (the Japanese word for "autumn leaves"), especially the momiji (Japanese maple) signals comfortable days and evenings—like "Indian summer" in New England—and a special relief from the record-breaking heat of this year's Japan summer. But RERF staff members have been working hard and have had little time for momijigari (Japanese maple hunting). We're pleased to be able to report some of the results of our staff's efforts.

Several new events for RERF were initiated during the second half of 2010 and are reported in this issue. For example, read about Dr. Truong-Minh Pham, the first recipient of a newly established RERF postdoctoral program. The first meeting of the Scientific and Ethics Committee for the Study of the F_1 Offspring of A-bomb Survivors was held, and an Epidemiological Training Workshop for Biologists was held for radiation biologists throughout Japan as a means of achieving communicating across different fields. An employee training session on Ethics and Protection of Study Participants in Medical Research was inaugurated, and RERF scientists participated in three special panel sessions held to publicize the scientific contributions of RERF, the first two at the 56th Meeting of the Radiation Effects Research Society and the third at the 52nd Annual Meeting of the American Society for Radiation Oncology. The RERF Open House in Hiroshima included a record-breaking attendance as well as an Open House Preview for RERF employees. A series of lectures on topics requested by employees was begun to provide a better understanding of ongoing RERF research among all employees, not just scientists. Finally, the first in what RERF plans to be a continuing series of Public Lectures to inform the public—including A-bomb survivors and their families, city officials, and other interested attendees—about the research and findings of RERF was held at the International Conference Center Hiroshima located in the Peace Memorial Park to a full audience of 230. The Public Lectures event (see cover photo) was judged to be a success and resulted in some good press coverage as part of RERF's efforts to improve public understanding and relations.

Please read other articles, including a report of the 45th Board of Directors Meeting held in Nagasaki, and condensations of two important scientific papers published recently in prominent journals. We were pleased to receive a visit in May by long-time ABCC-RERF supporter and former Director William "Jack" Schull who delivered an entertaining and informative lecture to RERF staff about his recollections of the early days of ABCC. Jack has promised a condensation of that lecture in the next issue of *Update* and in the meantime has provided a short and humorous Human Interest Note in this issue.

And yes—for those who have inquired—the world's economic situation, including the reduced Japanese yen to U.S. dollar ratio, has continued to impact adversely on the budget of RERF. As a nakama ("team") effort, our "belts have been tightened" and RERF staff have worked hard to reduce expenditures. For example, the replacement of the fallen-down, dilapidated gate at Hijiyama Hall (see the before and after photos) was the work of "Sunday carpenters" Chairman Toshiteru Okubo and yours truly (EBD).

We received a nice letter from Mr. Kenji Joji. As always, we appreciate your feedback and any suggestions you might have as to how we can improve the reporting of RERF's important work. So until the next issue of *Update*—Mata oidekudasai (goodbye and please come again)!



Evan B. Douple, Editor-in-Chief

Yuko Ikawa, Technical Editor

Hijiyama Hall gate before renovation (Winter 2009)

After renovation by "Sunday carpenters" (Autumn 2010)

Letter to the Editors

It is always a pleasure and joy to receive a copy of your RERF *Update*.

Your report of the 52nd Annual Meeting of the Japan Radiation Research Society which was hosted for the first time by Radiation Effects Research Foundation in Hiroshima was read with renewed interest. The devoted effort of Chairman Toshiteru Okubo who made this possible should be highly commended. This meeting, no doubt, has served to bring about a renewed recognition of the long-term longitudinal studies conducted by ABCC-RERF in Hiroshima and Nagasaki on the radiation effects on humans.

Being a faithful subscriber of National Geographic and an admirer of their DVDs on the wonders of our world, your news that a National Geographic Television film crew visited RERF in preparation of a documentary film of the A-bombing of Hiroshima and the research activities of RERF was a real delight to me.

Today's Chugoku Shimbun presented a very favorable report of the open house program at Hijiyama RERF where even on the first day there were a thousand visitors to the research facilities to learn more about the radiation effects on humans.

These to me are valuable avenues of favorable publicity of RERF and of dissemination of its research activities and results.

Gratefully yours,

Kenji Joji
Hiroshima, Japan

August 6, 2010, 65th anniversary of the A-bomb

45th Meeting of RERF's Board of Directors Convened in Nagasaki

Discussions Centered on Transition to a Juridical Person with New Management System

The 45th meeting of the Board of Directors was held in the Conference Room at Nagasaki RERF on June 21 and 22, 2010. At the meeting, the participants engaged in active discussions on RERF's transition to a public-interest incorporated foundation, in addition to such regular items as the activities report, activity plans, settlement of accounts, and working budget.

On behalf of the Japanese and U.S. governments, Mr. Yasunori Wada, Director, A-bomb Survivor Support Office, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW), and Dr. Joseph F. Weiss, Japan Program Manager, Office of International Health Studies, Office of Health, Safety and Security, U.S. Department of Energy (DOE), delivered opening remarks, they expressed their intentions to continue providing support to RERF, and with that the meeting's agenda was begun.

Dr. Toshiteru Okubo, RERF Chairman, opened with his status report for RERF, explaining the Scientific Council's review this year of the foundation's study program with a focus on the Department of Clinical Studies. He then referred to personnel actions among research scientists, reporting that, with the recent hiring of two research scientists in the Department of Statistics, the current number of research scientists reached 46, an increase of three compared with the number at the time of last year's Board of Directors meeting.

As one of RERF's ongoing research projects, dosimetry, Dr. Okubo reported that the Dosimetry Committee, established in April 2009, had completed dataset coordinate adjustment work and preparations to start the work of correcting the U.S. Army map distortion with use of orthophotographs and reconfirming coordinates of proximally exposed survivors through the use of neighborhood maps with shielding history information.

Regarding the response to the recommendations from the Senior Review Panel on Future Planning for RERF, Dr. Okubo reported that RERF was continuing discussions with the U.S. and Japanese governments concerning the foundation's future direction and the Hiroshima Laboratory's relocation. In terms of the status of preparations for transition to a public-interest incorporated foundation, Dr. Okubo reported the following: that MHLW and the Ministry of Foreign Affairs have authorized establishment of the Committee for Selection of First Councilors; and that the Hiroshima Laboratory hosted the initial meeting of the Committee for Selection of First Councilors in March 2010.

Dr. Okubo also explained that the employee training program, which continued for 18 months, concluded on April 21. The Executive Committee reviewed reports submitted by three policy-review groups, and based on the reports, established working groups to resolve the issues that had been raised, starting with the most practical.

Following the status report, Dr. Roy E. Shore, Vice Chairman and Chief of Research, reported that RERF received 39 external grants totaling ¥121,160,574, including the MHLW Scientific Research Grants. He also reported that last year RERF entered into a new research agreement with the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

Regarding international collaboration and PR activities, Mr. Takanobu Teramoto, Permanent Director, reported that a total of 15 RERF Directors and staff members participated in five international collaborative activities, including an activity related to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). RERF accepted, for observation and training, a total of 173 visitors from overseas, including those connected to the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) and the Nagasaki Association for Hibakushas' Medical Care (NASHIM).

Related to the items for deliberation and action, the Board of Directors approved, as presented, the FY2009 research activities report, the settlement of accounts and audit report, the FY2010 research activity plans of the F_1 clinical study, dosimetry revisions, and a circulatory disease study, as well as the FY2010 working budget.

In response to the Senior Review Panel's recommendations, comprehensive explanations were provided regarding such aspects of RERF operations as research themes, five-year research plans, project prioritization, and progress in expansion of international collaborative research, with the Directors expressing many valuable comments about these explanations.

On the second day, prior to proceeding with the meeting, Dr. Patricia R. Worthington, Director, Office of Health and Safety, Office of Health, Safety and Security, U.S. DOE, who arrived in Nagasaki the previous night, delivered an address stating that the U.S. and Japanese governments would continue to join forces in supporting the RERF project. After that, Mr. Mark S. Dieker, Consul for Political and Economic Affairs, U.S. Consulate in Fukuoka, who traveled to Nagasaki from Fukuoka, stated that the occasion represented his first participation in a Board of Directors meeting and that he wanted to learn as much as possible about the foundation's research activities.

In terms of status change to a public-interest incorporated foundation (PIIF), the most significant issue for RERF since last year, the Board of Directors last year approved a two-stage approach, as follows: an application for changes to the Act of Endowment would be submitted to the competent government agencies, and then an application for PIIF authorization would be submitted to the Cabinet Office in Japan. This year, there was discussion on the changes to the Act of Endowment, which constitute the first stage of the transition process. Based on the discussion at the latest Board of Directors meeting, several modifications were made and, as soon as relevant preparations are completed, an application for authorization as a juridical person with a new management system (special incorporated Civil Law Act foundation with councilors) will be submitted to the competent government agencies based on a Board of Directors mail ballot.

In addition, there was a comment requesting planning of an effective approach for recruitment of young talented researchers in connection with the ongoing policy of reducing personnel number. It was also reported that internal regulations were prepared regarding appointment of postdoctoral scientists, and that one research scientist was hired based on the funding received from NIAID.

Lastly, the Board discussed appointments involving two Scientific Councilors, whose terms concluded at the end of June. As a result of such discussions, the appointment of Dr. Kazuo Tajima, Director, Aichi Cancer Center Research Institute, to replace Scientific Councilor Yoshiharu Yonekura was approved. In the case of Scientific Councilor Marianne Berwick, however, since her successor's recommendation had not been forthcoming, it was approved in accordance with regulations that Dr. Berwick would continue to serve in her position until her successor's appointment.

The two-day meeting was concluded with a decision that the next meeting would be held in Hiroshima over the two days of June 21 (Tuesday) and 22 (Wednesday), 2011, and that the two days would be reserved for the Board of Councilors meeting, if approval of the new Articles of Incorporation is obtained in April 2011.

List of Participants

Directors:

Dr. Toshiteru Okubo, Chairman

Dr. Roy E. Shore, Vice Chairman and Chief of Research

Mr. Takanobu Teramoto, Permanent Director

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

Dr. Yasuhito Sasaki, Executive Director, Japan Radioisotope Association

Dr. Senjun Taira, President, Japan University of Health Sciences

Mr. James W. Ziglar, Former Sergeant at Arms of the United States Senate
Dr. James D. Cox, Professor and Head, Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center (Attendance by attorney)
Dr. Shelley A. Hearne, Managing Director, Pew Health Group, The Pew Charitable Trusts, Washington, DC

Supervisors:
Mr. Takashi Kohno, CPA/licenced Tax Accountant, Hiroshima General Law/Accounting Office
Mr. David Williams, Senior Financial Advisor, National Academy of Sciences

Co-chairman Scientific Council:
Dr. Takashi Yanagawa, Professor, The Biostatistics Center, Kurume University

Representatives of Supporting Agencies:
Mr. Yasunori Wada, Director, A-bomb Survivor Support Office, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW)
Dr. Kiwamu Nagoshi, Deputy Director, A-bomb Survivor Support Office, General Affairs Division, Health Service Bureau, MHLW
Mr. Kazuhiro Kanayama, Deputy Director, A-bomb Survivor Support Office, General Affairs Division, Health Service Bureau, MHLW
Dr. Yukiko Shinya, Group Leader, A-bomb Survivor Support Office, General Affairs Division, Health Service Bureau, MHLW
Dr. Patricia R. Worthington, Director, Office of Health and Safety, Office of Health, Safety and Security, U.S. Department of Energy (DOE)
Dr. Joseph F. Weiss, Japan Program Manager, Office of International Health Studies, Office of Health, Safety and Security, DOE
Mr. Mark S. Dieker, Consul for Political and Economic Affairs, U.S. Consulate Fukuoka
Dr. Warren R. Muir, Executive Director, Division on Earth and Life Studies, National Research Council (NRC), National Academy of Sciences (NAS)
Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS

RERF:
Mr. Eiji Akimoto, Chief of Secretariat
Dr. Evan B. Douple, Associate Chief of Research
Dr. Nori Nakamura, Chief Scientist
Dr. Kazunori Kodama, Chief Scientist
Mr. Douglas C. Solvie, Associate Chief of Secretariat

Participants of the 45th Board of Directors meeting (in front of lunch venue in Nagasaki)

RERF Held Its First Public Lecture for Citizens

On November 17 (Wednesday), RERF held its first Public Lecture for Citizens at the International Conference Center Hiroshima located in the Peace Memorial Park from 18:00 to 20:00. The objectives of the lecture were to explain to the general public, including A-bomb survivors, RERF's long-term research findings on health effects from atomic-bomb radiation in a straightforward manner, as well as provide an opportunity for the public to communicate with RERF. About 230 citizens filled the auditorium and participated in the lecture.

Following opening remarks by RERF Chairman Toshiteru Okubo, the public lecture comprised two talks. The first, titled "Radiation and Cancer Risk," was given by Dr. Kazunori Kodama, Chief Scientist, who explained on the basis of results from long-term health effects research the degree of increased risk of cancer including leukemia caused by radiation exposure. He also reported that about half of leukemia cases and roughly 10% of solid cancer cases among A-bomb survivors were attributable to radiation according to results from RERF's Life Span Study. The second talk, titled "Studies on Children of A-bomb Survivors Conducted Thus Far," was given by Dr. Nori Nakamura, Chief Scientist, who introduced results from studies of birth abnormalities, sex ratio, chromosome aberrations, mortality, and cancer incidence among the children of A-bomb survivors. He explained that genetic effects from parental exposure to radiation have not been observed thus far.

Those two talks were followed by a question-and-answer session, during which a number of inquiries were made by the audience including an A-bomb survivor regarding associations between radiation and disease. The lecture concluded with closing remarks by Vice Chairman and Chief of Research Roy E. Shore, and several audience members remained eagerly asking questions, which indicated that citizens have a high interest in RERF's research findings.

IAEA Director General Yukiya Amano Visits RERF

In the morning of August 6, Mr. Yukiya Amano, Director General of the International Atomic Energy Agency (IAEA), paid a visit to RERF's Hiroshima Laboratory. Arriving at the RERF front entrance, Mr. Amano was welcomed by Chairman Toshiteru Okubo and Vice Chairman and Chief of Research Roy E. Shore. Since RERF's Open House event was ongoing, Mr. Amano was first guided to the event's display panels and was provided with explanations about the history of ABCC-RERF and the foundation's activities, including contributions the organization has made to IAEA as part of its international collaborative activities. Mr. Amano toured the research departments, and then in the Chairman's Office, Dr. Shore provided him an explanation about the foundation's recent research achievements. Mr. Amano expressed appreciation for RERF's scientific contributions to IAEA's development of protection standards for nuclear power workers.

In the afternoon of the same day, at Hiroshima Red Cross Hospital and A-bomb Survivors Hospital (whose director is Dr. Hiroo Dohy, Chairman of the Hiroshima International Council for Health Care of the Radiation-exposed [HICARE]), IAEA and HICARE exchanged a memorandum of understanding for collaborative activities in the area of medical care of those exposed to radiation, with the aim of utilizing the expertise and experience regarding A-bomb survivor medical care accumulated in Hiroshima for support of the radiation exposed worldwide. The joint activities are to include personnel training, collaborative research, educational activities, and information exchange, with the expectation that RERF will contribute to the project.

IAEA Director General Yukiya Amano (second from right) touring RERF with guidance from Chairman Toshiteru Okubo (right)

Public Affairs Officer at the U.S. Consulate General Osaka-Kobe Visits RERF

On October 1, 2010, Mr. Gregory W. Kay, Public Affairs Officer, and Mr. Keizo Sanuki and Ms. Mari Matsumura, from the Public Affairs Section at the U.S. Consulate General Osaka-Kobe, visited RERF in Hiroshima. During the visit, Mr. Kay asked several questions while listening intently to explanations about RERF's history, overview, and research activities provided by Permanent Director Takanobu Teramoto, Associate Chief of Secretariat Douglas Solvie, and Chief of Statistics Harry Cullings. Mr. Kay and the two members of his staff were then taken on a tour of RERF's facilities.

Mr. Gregory W. Kay, Public Affairs Officer at the U.S. Consulate General Osaka-Kobe (center), touring RERF with guidance from Chief of Statistics Department Harry Cullings (right)

Staff News

We are pleased to report that **Tomonori Hayashi**, Chief of the Immunology Laboratory in the Department of Radiobiology/Molecular Epidemiology (RME) since 2005, has been promoted to Assistant Department Chief of RME as of 1 July 2010. Dr. Hayashi has been a research scientist at RERF since 1990, has been recently leading research on immunogenomics, and is a principal investigator on two projects in the RERF radiation immunosenescence study supported by the U.S. National Institute of Allergy and Infectious Diseases.

We are also pleased to report that **Truong-Minh Pham** was appointed as the first recipient of a new postdoctoral scientist fellowship program recently initiated and advertised by RERF. We have asked Dr. Pham to write a brief introduction about himself.

Truong-Minh Pham, MD, PhD

I spent my childhood in a small village in the countryside in Vietnam. My earliest memories are of the smell of the soil of the rice fields. In the harvest season, I followed farmers reaping rice in the field and used a grapefruit as a soccer ball. I played with other boys on the rice fields. It was a peaceful and enjoyable time of my life.

Truong-Minh Pham, Postdoctoral Scientist

When I was high school student, I did not want to be a doctor like my parents had hoped. I first thought about entering a natural science study program. But finally I entered a medical college and received an MD. Afterwards, I spent years training to become an ear-nose-throat specialist, including one training year in a clinical residency in the Department of Otorhinolaryngology, at the University Hospital, Lille City, France. I then served three years as a clinician and lecturer in Thai Nguyen Medical College from where I had received my MD.

My life certainly changed when I came to Japan to learn epidemiology. I started epidemiological work by being involved in the Japan Collaborative Cohort Study. After finishing my doctorate from the University of Occupational and Environmental Health, I was awarded a postdoctoral fellowship from the Japan Society for the Promotion of Science to continue my research work in epidemiology.

RERF has traditionally a good reputation in statistics and epidemiology. Thus, I am very grateful and fortunate to be accepted as a postdoctoral scientist in the institute. It is a special opportunity to meet RERF staff, and to learn many research ideas from them. I just moved in to the RERF Department of Epidemiology at the beginning of September, 2010. I hope that I can contribute significantly to the research work of the institute.

Visiting Scientsts

RERF was very fortunate to have several ABCC and RERF former employees and consultants visit for various times during the past six months in order to provide consultation and to engage in some collaborations with RERF scientists. Those visiting scientists included former employees Dr. **William Schull** (President, The Schull Institute), Dr. **Dale Preston** (Chief Scientist, HiroSoft International Corporation), Dr. **Donald Pierce** (Professor Emeritus, Oregon University), and Dr. **Robert Delongchamp** (Professor of Epidemiology, University of Arkansas for Medical Sciences), and current member of the partnership between RERF and the University of Washington Dr. **C. Y. Wang** (Full Member, Program in Biostatistics and Biomathematics, Fred Hutchinson Cancer Research Center).

Visiting Student Researchers

We are from Latvia. It is the one of the Baltic States (Estonia, Latvia, and Lithuania) and is located in Northeastern Europe on the east coast of the Baltic Sea. We had the wonderful opportunity to visit RERF, to become acquainted with the methods of radiation research used here, and to acquire new skills in this area of research. The new knowledge will help us in our daily work with the Chernobyl clean-up workers. We spent two months (30/09/2010–04/12/2010) in the RERF Department of Radiobiology/Molecular Epidemiology.

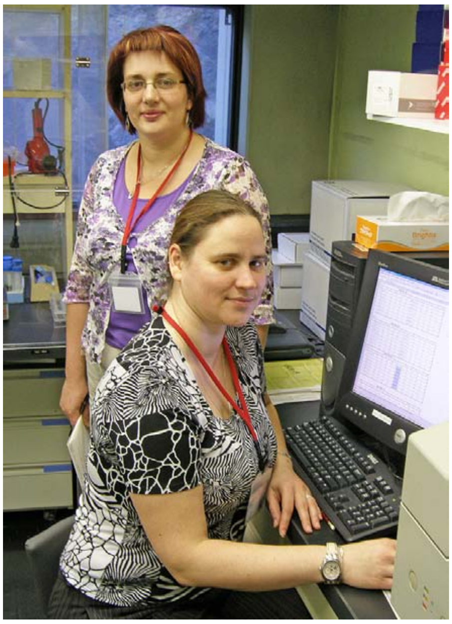
Inese Martinsone

After graduating from the University of Latvia with a MSc in chemistry I started working in Riga Stradins University (RSU) (previous Medical Academy of Latvia) in 1997 as a researcher in the Institute of Occupational and Environmental Health's Laboratory of Hygiene and Occupational Diseases. My work duties focused on analyzing different chemical substances in human tissues (i.e., changes in metal levels in Chernobyl clean-up workers' blood and hair samples) and work-place air samples. I was involved in interesting research related to my chemical background and I added knowledge in biochemistry, hygiene, occupational medicine, and toxicology. In this year (2010) I wrote my PhD thesis in my speciality of occupational and environmental medicine. Research is one part of my duties; the other part is educational work. I am working as a lecturer in RSU and teach public health students and postgraduate students.

Jolanta Cirule

I am working as an occupational physician in an out-patient department of the Center of Occupational and Radiological Medicine of P. Stradins Clinical University Hospital in Riga and as a lecturer in Riga Stradins University. The Center of Occupational and Radiological Medicine conducts follow-up of the Chernobyl clean-up workers of Latvia and collects the data about the Chernobyl clean-up workers in the Latvian State Register for persons who have received ionizing radiation exposure in Chernobyl and for patients with occupational diseases.

We both want to express our gratitude to the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) and RERF for the opportunity to take a part in the RERF Training Program, to all staff of RERF for accepting and hosting us, and to the staff of the Department of Radiobiology/Molecular Epidemiology for their collegial collaboration, especially to Dr. Tomonori Hayashi, who was our teacher and supervisor.



Dr. Jolanta Cirule (front) and Dr. Inese Martinsone

Awards Received by RERF Scientists

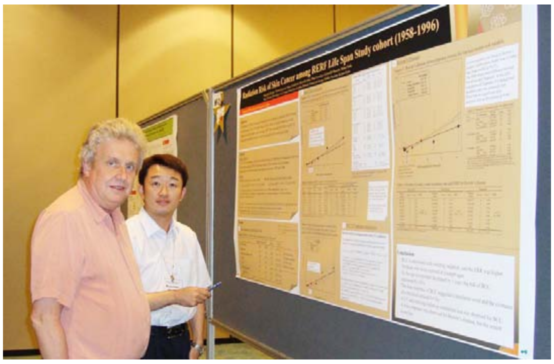
Upon Receiving the New Investigator Award

Munechika Misumi, Research Scientist
Department of Statistics

I recently received the New Investigator Award at the American Statistical Association (ASA) Conference on Radiation and Health, held on June 13–16, 2010, in Annapolis, Maryland. I made a presentation titled "Radiation Risk of Skin Cancer among Members of the RERF Life Span Study (LSS) Cohort of Atomic Bomb Survivors," speaking mainly about the statistical analysis collaboratively conducted between the RERF Department of Epidemiology and the U.S. National Cancer Institute (NCI).

I had heard that many experts in radiation epidemiology throughout the world would participate in the conference, and I was therefore expecting to discuss statistical aspects of radiation risk analysis with them, especially because the event was sponsored by the ASA. However, the conference turned out to include scientists from a wide variety of disciplines engaged in radiation research. In addition to radiation epidemiologists, there were radiobiologists and biostatisticians from the NCI and other radiation research organizations in the U.S., Germany, England, and other countries, technicians from radiotherapy device manufacturers, and physicians. A great variety of sessions were held including such themes as medical radiation effects on cancer and non-cancer diseases, radiation exposure among medical radiation workers, the latest technologies in radiotherapy devices, low-dose radiation exposure, and genetic susceptibility to radiation.

Since it has been reported that radiation dose response for skin cancer in the LSS cohort has a threshold, many scientists asked me about this topic. Scientists from America and Europe were surprised to find out how small the number of cases of skin cancer is in the RERF study cohorts, and how relatively rare the disease is in the Japanese population. I felt great pride in being a member of RERF when I realized that everyone knew about RERF when I introduced myself, when Dr. Harry Cullings and Dr. Dale Preston spoke about RERF and its research at the wrap-up session and the reception party, respectively, and when it became apparent how widely RERF is acknowledged throughout the world as the center of radiation health research.



Dr. Dale Preston (left) and Munechika Misumi in front of his presentation poster

In conclusion, this was the first project for which I have actually analyzed data at RERF since I stepped into the field of radiation health effects two years ago. In dealing with unique statistical models of radiation risk analysis for the first time, I received much advice from Dr. Hiromi Sugiyama, Dr. Fumiyoshi Kasagi, and others from the Department of Epidemiology, my seniors at the Department of Statistics including Dr. Preston, Dr. Kyoji Furukawa and Dr. John Cologne, and from Dr. Roy Shore, as well as from Dr. Kiyohiko Mabuchi and Dr. Elaine Ron at the NCI. I was able to manage the presentation thanks to such individuals. What I did for the study is conduct statistical analysis and discuss its interpretations with other researchers, but I have come to realize that so many people are involved in a study, including the pathologists who collect data. Since I just happened to be a newcomer to the association that organizes the ASA biennial meetings and was thus eligible for the New Investigator Award, I was originally reluctant to emphasize the fact that I won the award. However, I decided to contribute this article to express my gratitude to everyone who has guided me and assisted me in this study. I would like to conclude by requesting everyone's continued support and guidance.

Upon Receiving the Poster Award by the International Association of Cancer Registries

Midori Soda, Assistant Chief
Department of Epidemiology, Nagasaki

With the main theme of "Society and Cancer Registration: Towards Harmonization," a three-day meeting of the International Association of Cancer Registries (IACR) was held October 12–15, 2010, in Yokohama, Kanagawa Prefecture. This marked the 32nd such scientific meeting, which is held annually in different countries on five continents in rotation. It was decided at the 2007 meeting in Slovenia that the venue for the 2010 meeting would be Japan. Subsequently, an organizing committee was established under the leadership of Dr. Tomotaka Sobue, from Japan's National Cancer Center, and I was engaged in preparations for the meeting as a committee member.

Even though I was concerned that participants from abroad would hesitate to attend the meeting due to the recent appreciation of the yen, the meeting gathered more than 250 people and was concluded successfully. This year's meeting was attended by an unusually large number of participants from Asian countries, in addition to many from the continents of Europe, Africa, and America.

One of the features of such meetings is the presentation of poster awards. Almost every year, Dr. Hans Storm from Denmark serves as presenter and introduces awardees in a light and humorous manner, making me laugh even though I am not very good at English. Since attending the 1998 meeting in Atlanta for the first time, I have been captivated by his presentations. Therefore, I have prepared posters and attended the meeting every single year in the hopes of receiving the poster award just once.

Posters prepared by Japanese researchers in the past were lampooned as patchwork. Since a large-scale printer was introduced at RERF six to seven years ago, however, followed by assignment to the Epidemiology Department in Nagasaki of Mr. Mikio Soejima, who would put professional graphic designers to shame, our posters have been improved visually. I then worked on the poster content. From among a total of 147 posters submitted to the association for this year's meeting, my poster, the preparation of which Mr. Soejima devoted himself to on my behalf, was remarkable even from an objective standpoint. Even so, I never dreamed of receiving the poster award, because the selection committee, comprised of at least 10 members, was to evaluate each of the poster presentations on the basis of six points for content and four points for visual presentation.

Midori Soda (right) with Dr. Adriano Laudico of Philippines in front of her presentation poster

At the close of the meeting on the third day, Dr. Storm was announcing awardees. When he called out the name "Midori Soda," I could not immediately believe that I had received the award. I felt uncomfortable at first because a Japanese researcher had been granted the poster award at the meeting held in Japan. When Dr. Brenda Edwards (U.S. National Cancer Institute; NCI), President of IACR's Executive Board, presented a certificate of merit to me, however, I felt genuinely delighted. This was my 11th attempt. The title of my award-winning poster was "Decreased mortality from prostate cancer observed in Sasebo City, Nagasaki Prefecture, with introduction of PSA screening."

Upon Receiving the Shichijo Prize from the Japan Thyroid Association

Misa Imaizumi, Chief, Division of Radiology
Department of Clinical Studies, Nagasaki

On November 12, 2010, I was awarded the 39th Shichijo Prize at the 53rd Annual Meeting of the Japan Thyroid Association. This prize was established to encourage young scientists to actively pursue their research and is awarded to a researcher of less than 45 years of age who has published top papers concerning thyroid disease over the years. I am both pleased and humbled to win such a prestigious prize, which had also been awarded to Dr. Shigenobu Nagataki, former RERF chairman (5th recipient, 1976).

I have studied thyroid disease since I was a graduate student at Nagasaki University. I was engaged in basic research using animal models as a postgraduate researcher at Nagasaki University and during my overseas study in the United States at Mt. Sinai School of Medicine. Thereafter, I had the opportunity to conduct research in the field of clinical epidemiology at RERF. My main area of interest is thyroid disease in A-bomb survivors. I am pursuing my research thanks to the cooperation of the Adult Health Study (AHS) participants and with the assistance of many people, including members of the Departments of Clinical Studies in Hiroshima and Nagasaki, as well as the Departments of Statistics, Epidemiology, and Information Technology. Our studies during 2000–2003 showed that effects of A-bomb radiation are still observed in the form of malignant and benign thyroid nodules in A-bomb survivors alive more than 50 years after the bombings. We also showed that the risk of ischemic heart disease may increase in the AHS participants diagnosed as having subclinical (minor) hypothyroidism.

A paper reporting those findings recently provided me with the opportunity to participate in a collaborative study of 11 cohorts comprising a total of 55,000 subjects throughout the world. The collaborative study demonstrated increased incidence and mortality rates of cardiovascular disease among patients with subclinical hypothyroidism (Rodondi N, … Imaizumi M, *et al*. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; 304[12]:1365–74).

I would like to express my sincere appreciation to the many people whose support enabled me to be awarded the prize. I will continue to work hard with a focus on thyroid disease. Your kind guidance would be much appreciated.

Misa Imaizumi with her award

Employee Training on Ethics and Protection of Study Participants in Medical Research

Takanobu Teramoto, Permanent Director

It is probably common knowledge among researchers that an ethical review is required before initiation of medical research. This cannot be underestimated, since any scientific project involving the study of humans may not start without an ethics committee's approval. On the other hand, we might not have had the opportunity to think deeply of this issue's historical and philosophical background. In addition, even though some administrative and technical staff members daily meet study participants or handle their clinical or other epidemiological data, or blood and other biospecimens, they may have had little opportunity to be directly involved in ethical review of research. I recently served as lecturer for the employee training on ethical issues involved in medical research—possibly the first of such training at RERF.

The idea of having this training was born when the U.S. Department of Energy (DOE) Panel, consisting of six highly-qualified experts from the U.S. and Japan, reviewed the status of human subject protection at RERF in June 2009. Although the Review Panel concluded that "RERF demonstrates an extremely high level of commitment to protecting the rights and welfare of its unique research participant population," it also pointed out a few items for improvement, in particular employee training.

First, it was necessary to find training materials. Since RERF's research program is regulated by the U.S. and Japanese laws/guidelines, it means that the training needs to satisfy both the U.S. and Japanese requirements. For this reason, I began collecting, studying, and editing work of relevant materials obtained in both the U.S. and Japan. Fortunately, Ms. Elizabeth White of DOE encouraged me to participate in a national convention of those involved in medical research ethics in the U.S. in November 2009, and I took the opportunity to attend and to collect U.S. materials. Using as a guide the DOE's Human Subjects Protection Resource Book, I decided on the training outline, which consisted of the following five topics: 1) Introduction, 2) History, 3) Philosophy, 4) Regulation, and 5) RERF's policy and procedures.

Takanobu Teramoto, Permanent Director

The next step was preparation of Japanese materials. Thanks to an online search, I found "RecNet Fukuoka," which posted excellent reference materials online. This website was written in a clear style, and included detailed explanations about some of the five training items mentioned above. It also included substantial overseas materials translated into Japanese in an excellent way. The website was reportedly developed by professors at Kyushu University with support of a Ministry of Health, Labour and Welfare (MHLW) research grant.

The first training sessions in Japanese were held in Nagasaki on March 23, training time was one and a half hours, and in Hiroshima on April 20 and 23.

A lecture in English was given in Hiroshima on July 9. There was quite a large turnout for each of the three training sessions, and almost all employees—both fulltime and temporary staff—have participated in one of the sessions. The video-recorded lectures have been made available for viewing on the RERF's internal website for employees who could not attend the lectures. I hope that, for their continued study, employees will use the training material and the reference sources on research ethics available on the RERF internal website that was also developed on this occasion.

For each session, I conducted a questionnaire survey among the training participants and many of them responded. The questionnaire consisted of the following simple questions: 1) What did you find difficult to understand?; 2) What did you find instructive?; 3) What did you find not instructive?; 4) What would you like future sessions to include?; and 5) Any other comments? The free-entry questionnaire on an anonymous basis served to provide frank opinions from many participants and I used them to improve the next session.

In addition, to make the best use of the feedback provided in the questionnaire surveys for the next year's training, I plan to divide the training into courses under specific themes like ethical review of research protocols, informed consent, and protection of personal information, so that employees will be able to participate in one or more courses depending on their individual needs. Also, many employees have requested that specific examples be shown in the training session. I therefore would like to design future training courses with some case studies under specific themes to be discussed by the lecturers and trainees.

I would like to take this opportunity to express my sincere thanks to all RERF employees who participated in the training, and all my colleagues, who helped prepare for the training. And I would like to express my deepest gratitude to Dr. David Thomassen, Ms. White, Dr. Peter Kirchner and other officials in DOE, who gave me guidance to conduct the training and the opportunity to attend workshops on the subject of ethical research in the U.S. I am also grateful to my National Academy of Sciences colleagues, whose long-time support of research ethics is critical to RERF's success.

First Meeting of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors

Saeko Fujiwara, Chief
Department of Clinical Studies, Hiroshima

The first meeting of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors was held in the Auditorium at Hiroshima RERF on July 7, 2010, during which the committee discussed the proposed F_1 clinical study (longitudinal study). As in the case of the previous Health Effects Study of the Children of A-bomb Survivors (cross-sectional study), which was conducted between 2000 and 2006, the committee consisting of outside specialists was established to verify in advance the scientific and ethical appropriateness of the study plan and ensure the study's transparency. Based on the original study, the longitudinal F_1 clinical study aims to conduct a long-term study on whether parental A-bomb radiation exposure affects development of disease in offspring. The study will conduct health examinations, in which about 12,000 A-bomb survivors' children are to participate every four years.

In the original cross-sectional study, 24,673 persons, primarily the A-bomb survivors' children in Hiroshima and Nagasaki, were contacted to request their participation in the study, with 11,951 actually participating. The study results were announced in March 2007 as the "Report on the Health Effects Study of the Children of A-bomb Survivors" by the Joint Scientific and Ethics Committee for the Health Effects Study of the Children of A-bomb Survivors. The report concluded that, "In analysis of the data from the current study, when lifestyle diseases in children were combined, no evidence suggesting increased risk associated with parental radiation exposure was observed." At the same time, however, there was a proposal from the joint committee regarding the necessity of a longitudinal study. In addition, the RERF Scientific Council and the Senior Review Panel on Future Planning for RERF, two advisory bodies consisting of U.S. and Japanese third-party members, recommended that the F_1 clinical study be continued. The RERF's F_1 Clinical Study Working Group then had repeated discussions on planning a longitudinal study, resulting in the holding of this first meeting of the Scientific and Ethics Committee for the

Clinical Study of the F_1 Offspring of A-bomb Survivors.

The agenda started with greetings from Committee Chairman Tadao Shimao. I, as Chief of the Department of Clinical Studies, then presented the outline and results of the original F_1 clinical study, which was followed by Senior Scientist Waka Ohishi's presentation on the outline of the proposed longitudinal F_1 clinical study. Moderated by Chairman Shimao, there was a lively Q and A session on scientific aspects of the long-term follow-up study, including the study's significance, statistical power, hypothesis, subjects, schedule, health examination's contents, diagnostic criteria, and storage of biological samples. Moderated by Committee Vice Chairman Hiraku Takebe, the committee next discussed such ethical issues as RERF's approach to ethics, contents of the informed consent form, and obtaining of informed consent for potential epigenome research in the future. The committee ultimately approved initiation of the study, on the condition that the explanatory notes in the informed consent form would be partially revised on the basis of ethical considerations. The study started in October, and we are receiving substantial support from the Department of Information Technology, the Department of Epidemiology, and others. With the additional F_1 participants, the number of health examinations conducted per year is expected to roughly double.

Members of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors

Tadao Shimao (Chairman), Consultant, Japan Anti-Tuberculosis Association
Hiraku Takebe (Vice Chairman), Fellow, Kinki University Atomic Energy Research Institute
Hirotsugu Ueshima, Special Contract Professor, Lifestyle-related Disease Prevention Center, Shiga University of Medical Science
Takashi Kawamoto, Professor, Graduate School of Education, The University of Tokyo
Shinsuke Kimura, Attorney, Kimura Shinsuke Law Office
Steve Wing, Associate Professor, Department of Epidemiology, School of Public Health, University of North Carolina
Kazuo Tajima, Director, Aichi Cancer Center Research Institute
Masao Tomonaga, Director, Japanese Red Cross Nagasaki Atomic Bomb Hospital
Hiroo Dohy, Director, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital
Ohtsura Niwa, Professor Emeritus, Kyoto University
Taisei Nomura, Professor Emeritus, Osaka University
Norihiko Hayakawa, Professor Emeritus, Hiroshima University
Katsumi Furitsu, Visiting Lecturer, Hyogo College of Medicine
Eiji Maruyama, Professor, Graduate School of Law, Kobe University

First Meeting of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors

Epidemiological Training Workshop for Biologists

Nori Nakamura, Chief Scientist

The training workshop, held at the Radiation Effects Research Foundation (RERF) on September 2–3, 2010, turned out to be a lively gathering, with participation by 32 outside researchers and more than 20 RERF researchers. The event was organized as part of the activities of the Council of Radiation Effects Research Organizations, consisting of Hiroshima University, Kyoto University Radiation Biology Center, Nagasaki University, the National Institute of Radiological Sciences (NIRS), and RERF, established to facilitate mutual understanding and collaboration among radiation effects research organizations. The event's objectives were to allow biologists and epidemiologists an opportunity to become acquainted with each other and engage in conversation on their common theme of radiation risk.

Starting at 1 p.m. on the first day, RERF Chairman Toshiteru Okubo gave opening remarks and the workshop participants introduced themselves. Dr. Kotaro Ozasa, Chief of the Department of Epidemiology at RERF, then delivered two lectures titled "Methods of epidemiological study" and "A brief outline of the study results of atomic-bomb survivors: risk of leukemia, solid cancers, and non-cancer diseases," each followed by a question-and-answer session. Subsequently, a reception was held at RERF's Hijiyama Hall. This provided biologists with a good opportunity to feel closer to RERF epidemiologists and statisticians with whom many of the biologists typically have few interactions.

On the second day of the workshop, the epidemiologists, statisticians, and biologists participated in a discussion session. Questions had been solicited from expected workshop participants beforehand, and a respondent for each question was identified, either on a voluntary basis or by recruitment. The trial arrangement turned out to be a success. The first pre-submitted question from the biologists, "Does age-dependence in breast cancer risk among A-bomb survivors exist?," was responded to by Dr. Yukiko Shimizu (RERF) in an explanation that referred to two papers—Land *et al.*'s 2003 paper reporting the presence of dependence of age at exposure and Preston *et al.*'s 2007 paper reporting no such dependence—to the effect that the studies used different observation periods and case ascertainment methods, and thus different numbers of cases, which resulted in a partial discrepancy in the conclusions they drew. As for the next question, "Can useful information be derived from censored animal experiments without observing animals throughout their lives?," Dr. Michiaki Kai (Oita University of Nursing and Health Sciences) offered his commentary. As to the question "How should competing causes of death be assessed in animal experiments?," Dr. Kazutaka Doi (NIRS) offered an explanation titled "Survival-time analysis and competing risks." I was reminded again of how difficult cross-field communication is and also felt that RERF biologists probably are not fully taking advantage of their fortunate work environment, which allows them to consult with statisticians any time they want. The final question theme, "Radiobiological interpretation regarding site-specific radiation risk, shape of dose-response relationships, and effects by aging and age at the time of exposure to radiation," the ultimate query posed by the epidemiologists, was addressed by Dr. Yoshiya Shimada (NIRS) and myself.

Although there was some room for improvement in terms of operation of the event, a wide variety of people—from graduate students to retired scientists—participated in the workshop, and I therefore believe that our initial objectives were achieved. Both fields of radiation biology and radiation epidemiology have, to this point in time, addressed similar themes without having many opportunities to communicate with each other. The workshop made it clear that the gap between the two fields of research is wider than originally many thought. I felt that RERF should take the initiative in creating opportunities to enhance "cross-field communication" on an ongoing basis, not only outside RERF, but also within to ensure that researchers in different fields can communicate effectively.

In conclusion, I would like to express my deepest appreciation to both those inside and outside RERF who helped organize the workshop.

RERF Studies and Results Highlighted in Presentations at Two Annual Scientific Meetings

Evan B. Douple, Associate Chief of Research

In an effort to encourage more participation by epidemiologists in the annual meetings of the Radiation Research Society and to increase dialogue between radiation biologists or other radiation scientists and epidemiologists, Dr. Shore and I worked with the meeting organizers of the **56th Meeting of the Radiation Research Society** to plan and recruit speakers for two symposia for the meeting held in Maui, Hawaii, September 25–29. The first symposium, titled "Studies of Radiation Susceptibility to Cancer: Where Do We Stand?," focused on genotyping, statistical, phenotypic, and functional assays as means to determine radiation susceptibility to cancer. The opening speaker was RERF's **Tomonori Hayashi** who presented a paper "Molecular epidemiology of radiation susceptibility to cancer among atomic-bomb survivors." His presentation focused on RERF's progress in analyses of: 1) radiation effects on immunological and somatic mutability markers (phenotypic effects); 2) genetic polymorphisms responsible for inter-individual variation of the biomarkers (genotype-phenotype associations); and 3) risk estimation of cancers on the basis of gene/radiation interactions (genotypic effects). The second symposium, titled "Risk from *In Utero* Radiation Exposure" focused on recent epidemiology and radiobiology studies following *in utero* exposure to the A-bombs in Japan, the ^{131}I emissions from the Chernobyl accident, and to occupational sources. The first speaker, RERF's Vice Chairman and Chief of Research **Roy Shore**, summarized the RERF findings in a paper titled "Are those exposed *in utero* the most sensitive population?—the Japanese A-bomb experience." The fourth and final speaker, RERF's Chief Scientist **Nori Nakamura**, described results of RERF's radiobiology studies in animals and humans related to *in utero* exposures in "Fetuses are not little children: Just ask their hematopoietic stem cells."

ASTRO is a society of approximately 10,000 North American and international members composed of radiation oncologists, nurses, therapists, medical physicists, and biologists. The **52nd Meeting of ASTRO** (American Society of Radiation Oncology) was held in San Diego, California, October 31–November 4. Early in the year, a member of the meeting's Steering Committee, former RERF Scientific Councilor, Dr. **Theodore DeWeese** (Johns Hopkins University School of Medicine) encouraged Dr. Shore and me to plan a panel to present at the 2010 ASTRO meeting that would highlight the scientific contributions of ABCC-RERF to the long-term radiation effects issues related to radiation exposures in the treatment of cancer patients. Such a panel was organized and was titled: "Hiroshima and Nagasaki 65 Years Later—Lessons Learned by the Radiation Effects Research Foundation That Are Helping Science, Physicians, Patients, and the A-bomb Survivors Today." After an introductory overview of the formation, mission, and major cohorts and studies of ABCC-RERF, **Roy Shore** discussed the epidemiological assessment of cancer risks in "What light do the cancer studies of A-bomb survivors shed on late effects from radiation therapy?" Chief Scientist **Kazunori Kodama** followed with a review of non-cancer risk assessment in "What and how important are the late non-cancer risks from radiation therapy (with special reference to heart disease risks among A-bomb survivors)?" I concluded the panel with a review of the laboratory science studies with emphasis on the work in the Departments of Genetics and Radiobiology/Molecular Epidemiology in "Genetic and molecular research contributions, challenges, and opportunities." We were pleased to learn that despite several ongoing parallel panels at the same time and a late-afternoon time slot, several hundred meeting participants filled the large lecture hall and showed an interest in hearing the latest scientific results from RERF's studies of a historic and unique cohort. Current Visiting Director Dr. **James Cox** was in the front row lending his support!

Evan B. Douple, Associate Chief of Research

Interaction Effects of Radiation and Smoking on Lung Cancer Incidence in the Life Span Study*

Kyoji Furukawa

Department of Statistics, Radiation Effects Research Foundation

*This article is based on the following publication that can be read in its entirety at the RERF website www.rerf.jp:

Furukawa K, Preston DL, Lönn S, Funamoto S, Yonehara S, Matsuo T, Egawa H, Tokuoka S, Ozasa K, Kasagi F, Kodama K, Mabuchi K. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. *Radiat Res* 174:72–82, 2010.

Introduction

Lung cancer is the most common cancer worldwide.[1] While lung cancer rates are largely determined by smoking patterns, medical, occupational, and environmental radiation exposures have also been shown to increase risks of lung cancer.[2] There is considerable interest, from biological and practical perspectives, in the joint effect of radiation and smoking on lung cancer. Lung cancer is the second most common cancer in the Life Span Study (LSS) cohort, and lung cancer incidence rates in the LSS have been known to be strongly associated with radiation, with an estimated excess relative risk (ERR) per Gy of 0.81 and excess absolute risk (EAR) of 7.5 per 10,000 person-year Gy.[3] Those estimates do not take into account a possible modifying effect of smoking on the radiation risk. While earlier analyses [4,5] of the LSS data were unable to describe sufficiently the nature of the interaction between radiation and smoking for lung cancer risk, due mostly to limited numbers of cases, the latest analysis by Pierce *et al*.[6] suggested that the interaction was sub-multiplicative and consistent with additivity.

The present study was based on lung cancer incidence data from a special pathology review that provided diagnostic confirmation on cases diagnosed between 1958 and 1999. A reassessment of smoking history data assembled from multiple sources provided enough detailed information needed to consider models in which the effect of cumulative amount smoked could be modified by smoking duration and intensity and to consider various types of generalized interaction models used in many other analyses of the joint effects of carcinogenic agents. In this study, we present the results from the effort to evaluate all types of lung cancer as a group.

Materials and Methods

Study population and case ascertainment

The LSS cohort includes 120,321 residents of Hiroshima and Nagasaki who were born prior to the atomic bombings in August 1945 and were still alive on October 1, 1950. For the present analyses, we excluded cohort members who could not be traced, had died, or were known to have had cancer prior to January 1, 1958 (8,396 subjects) or those with radiation dose estimates not available (6,521 subjects), resulting in a total of 105,404 eligible subjects.

A special pathology review provided diagnostic confirmation for lung cancer cases. The primary sources used to identify potential cases for the pathology review were the Hiroshima and Nagasaki tumor and tissue registries. Additional sources included the RERF autopsy program and death certificate data routinely obtained for LSS follow-up. The review considered cases diagnosed through the end of 1999, resulting in the followed-up ages ranging from about 12 to more than 100 and the ages at diagnosis from 27 to 104. An initial screening identified 5,711 LSS cohort members who were coded as having tumors of the lung or related regions. Three study pathologists independently reviewed those cases and developed a consensus diagnosis for each potential case. The reviews were based on all available information including tumor tissue slides pathology and clinical records, and death certificates. Lung tumors were diagnosed using the latest WHO diagnostic criteria.[7] The review identified 2,446 lung tumors including 2,368 cancers. Second primary or non-malignant tumors were excluded. The primary analyses described herein considered 1,803 primary lung cancer cases diagnosed among 105,404 cohort members, including 40,980 subjects (677 cases) with no information on smoking status prior to the diagnosis date.

Radiation dose and smoking information

Radiation dose estimates to the lung from an improved dosimetry system (DS02),[8] computed as the sum of the gamma-ray dose and 10 times the neutron dose, were used for these analyses. Most of the data on smoking habits of LSS cohort members came from a series of mail surveys conducted between 1965 and 1991. Information on smoking habits included amount smoked, duration of smoking, and, for past-smokers, when he/she stopped. Smoking history was summarized by indicators of smoking status (never-smoker, past-smoker, or current-smoker) at the time of the latest information, age started smoking, age stopped smoking, the average number of cigarettes smoked per day, and the year in which data on smoking were first obtained. Values were imputed for those subjects as the gender and birth cohort-specific mean values among smokers with complete information. Smoking information was available for 62% of the eligible cohort members. The amount smoked was imputed for 4% of those who indicated that they had ever smoked while the age at the start of smoking was imputed for 9.5% of this group.

Data organization for analyses

The risk analyses were based on incidence rates computed from a table of person-years and lung cancer cases stratified by age, sex, city, smoking, and radiation dose categories. The smoking categories were time-dependent. All cohort members were classified as unknown smoking status prior to the date at which they first provided information on smoking habits in order to avoid biasing risk estimates by overcounting person-years in known smoking-status categories.

As in all recent analyses of the LSS cancer incidence data, the analyses were limited to cases diagnosed among residents of the tumor-registry catchment areas. Because individual residence history data were not available for all cohort members, city, gender, age, and time-dependent residence probabilities estimated from the Adult Health Study (AHS) clinical contact data were used to compute migration-adjusted person-years.[9]

Statistical analysis

Smoking and radiation joint effects

These analyses focused on the joint effects of radiation and smoking in terms of risks relative to attained age (a), gender (g), and birth cohort (b)-specific baseline rates for non-smokers with no radiation exposure. That model can be written as $\lambda_0(a,g,b)\,RR(C,D)$ where RR is a relative risk function that depends on smoking-related variables (C) and radiation-dose-related variables (D). The smoking-related variables included years smoked (y), cigarettes smoked per day (c), and years since last known quitting (q) for past smokers, and other factors such as gender and birth cohort. The radiation-related variables included dose (d) and effect modifiers such as age at exposure (e), gender, and attained age.

The simplest joint effects model is the *additive ERR* model:

$$RR(C,D) = 1 + \phi(C) + \rho(D), \qquad \text{[Additive]}$$

where ϕ and ρ are functions that describe the ERR's for smoking- and radiation-related variables, respectively. Under this model, smoking and radiation have independent effects on the baseline rate for non-smokers. The most commonly used alternative to the additive ERR model is the *multiplicative ERR* model:

$$RR(C,D) = [1+\phi(C)][1+\rho(D)] = 1+\phi(C)+\rho(D)+\phi(C)\,\rho(D). \qquad \text{[Multiplicative]}$$

With this model, a given radiation exposure (or a given smoking history) increases the risk by the same proportion for any smoking history (or radiation exposure).

These two models are special cases of more generalized joint effect models, which we call the *generalized additive* and *multiplicative ERR* interaction models:

$$RR(C,D) = 1+\phi(C)+\rho(D)\omega(C), \qquad \text{[Generalized additive]}$$

$$RR(C,D) = [1+\phi(C)][1+\rho(D)\omega(C)], \qquad \text{[Generalized multiplicative]}$$

where ω is a function of smoking variables with $\omega(C) = 1$ for lifelong non-smokers. In these models, the effect of smoking on the radiation dose response is neither independent of dose (as in the simple additive model) nor constrained to be proportional to the main effect of smoking, $\phi(C)$ (as in the simple multiplicative model).

Additional models utilized in the statistical analyses are described in the manuscript and include a *Baseline rate (zero-dose, non-smokers) model,* a *Smoking effect model*, and a *Radiation effect model*. As in most recent work on risk modeling in the LSS,[3,10] radiation main effects, $\rho(d)$, were modeled as a product of a dose-response shape function, $\eta(d)$, and an effect-modification function $\varepsilon(a,g,e) = \delta_g a^{\beta}\exp(\gamma e)$.

Poisson regression maximum likelihood methods were used for parameter estimation, hypothesis testing, and the computation of confidence intervals (CI) for specific parameters. Model fitting was carried out using Epicure[11] and the generalized non-linear model package (gnm) in R.[12] We also used the Akaike Information Criteria (AIC)[13] for comparison of non-nested models involving different numbers of parameters.

Results

Data on smoking were available for about 60% of men and 64% of women. Roughly 85% of the men and 18% of the women who provided information on smoking habits indicated that they had ever smoked. The proportion of ever-smokers among men was similar over birth-cohort and radiation-dose categories. Women who were over 20 at the time of the bombs were somewhat more likely to have smoked than younger women, and the proportion of ever-smokers increased slightly with decreasing distance from the hypocenters (and, hence, with increasing dose). Men reported smoking about twice as many cigarettes per day (mean 19.6) as women (mean 10.6) and tended to start smoking younger (mean starting ages of 21 and 31.6, respectively). About one-third of ever-smokers reported having stopped smoking prior to the last survey to which they responded. By the end of follow-up, those who reported having stopped had smoked for roughly 20 years less than those who did not. Incidence rates were higher for current smokers than for never- or past-smokers. Crude rates for a given smoking category were about twice as high for men than for women and increased with increasing age at exposure (or decreasing calendar year of birth) as well as with radiation dose.

Non-smoker baseline rates and smoking effects

Smoking effects were modeled using ERR models and expressed relative to gender-specific baseline rates for non-smokers with allowance for radiation effects. The non-smoker baseline rates for men and women increased markedly with attained age. There was a statistically significant gender difference in the attained-age trend (P = 0.05). The increase was

Table 1. Parameter estimates for smoking effects (Panel A) and radiation effects (Panel B) and modifying effects with 95% (likelihood-based) confidence intervals

A. Smoking effect

Effect	Simple additive	Generalized multiplicative
ERR per 50 pack-years (born in 1915)		
Gender-average	5.32 (4.10,6.70)	4.69 (3.65,5.94)
Male	3.48 (2.40,5.00)	3.60 (2.60,5.10)
Female	7.16 (5.20,9.70)	5.77 (4.10,7.90)
Female:Male ratio	2.15 (1.30,3.40)	1.61 (1.00,2.50)
Birth-cohort effect (% change per decade decrease in birth year)		
% per decade decrease in birth year	0.38 (18%,61%)	0.33 (15%,54%)
Smoking-duration effect (log-linear)		
Log(duration/50)	-0.30 (-1.26, 0.60)	-0.24 (-1.20, 0.69)
Log(duration/50) squared	-2.58 (-5.30,-0.63)	-2.51 (-5.20,-0.56)
Years since quitting effect		
Power of years since quitting plus 1	-0.50 (-0.90,-0.29)	-0.47 (-0.77,-0.27)

B. Radiation effect

Effect	Radiation only	Simple additive	Simple multiplicative	Generalized additive	Generalized multiplicative
ERR per Gy (age 70, age-at-exposure 30, never-smoker)					
Gender-averaged	0.83 (0.55,1.20)	0.98 (0.59,1.50)	0.68 (0.43,1.00)	0.65 (0.31,1.10)	0.59 (0.31,1.00)
Male	0.34 (0.15,0.60)	0.69 (0.26,1.30)	0.31 (0.13,0.56)	0.30 (0.01,0.56)	0.29 (0.10,0.62)
Female	1.31 (0.83,1.90)	1.27 (0.73,2.00)	1.06 (0.64,1.60)	1.00 (0.77,2.30)	0.90 (0.47,1.50)
Female:Male ratio	3.82 (2.00,9.00)	1.85 (0.84,5.10)	3.44 (1.70,9.00)	3.38 (1.40,11.0)	3.13 (1.60,7.00)
Attained-age effect (power)					
Attained age	-2.00 (-4.0,-0.03)	-2.70 (-4.7,-0.6)	-2.50 (-4.5,-0.4)	-3.05 (-5.2,-0.9)	-2.78(-4.9,-0.7)
Age-at-exposure effect (% change per decade increase)					
Age at exposure	21% (-6%,55%)	31% (-2%,77%)	26% (-5%,69%)	50% (9%,111%)	30% (-3%,77%)
Smoking-intensity effect (effect modification)					
Packs per day	–	–	–	10.20 (4.6,17.0)	9.20 (3.8,15.0)
Packs per day squared	–	–	–	-15.30 (-30.0,5.4)	-16.6 (-30.0,-6.6)
Model and fit summary information					
Deviance	9815.5	9428.7	9425.1	9415.7	9410.3
Parameters	14	26	26	28	28
AIC	9843.5	9480.7	9477.1	9471.7	9466.3

well-described using a simple Armitage-Doll-like model in which the rates were proportional to attained age to the power 5.6 (95% confidence interval [CI]: 5.2, 6.1) with age-specific rates for women being 61% of those for men (95% CI: 48%, 80%). Age-specific rates exhibited a statistically significant (P < 0.001) increase of 17% (95% CI: 10%, 25%) per decade in year of birth. The final baseline rate model allowed a more rapid increase in the risk at younger ages, which resulted in a statistically significant improvement in the fit (P < 0.001).

Table 1A presents smoking-effect parameters estimated using the generalized multiplicative and simple additive radiation-smoking interaction models, together with modifying effects of birth year and smoking duration. Assumptions about the nature of the interaction had little effect on the smoking risk estimates. With the generalized multiplicative model, the gender-averaged ERR associated with smoking 20 cigarettes per day for 50 years (i.e., 50 pack-years) for an unexposed individual born in 1915 was estimated to be 4.7 (95% CI: 3.6, 5.9). This was only slightly lower than that of 5.3 based on the additive model. The ERR associated with smoking was statistically significantly higher for women than for men (P = 0.02), with the gender difference being greater with the additive model estimates. Age-specific ERRs for a given smoking history exhibited a statistically significant increase (P < 0.001) with decreasing birth year without an indication of a gender difference (P = 0.4, data not shown).

In our modeling of the smoking ERR, the pack-year effect was allowed to vary depending on smoking duration (P = 0.001). While the pack-year effect was highly statistically significant, the negative coefficients for the duration effects imply that the increase in rates is not linear in years smoked and that this departure from linearity becomes more marked at longer durations. Under this duration-modified pack-year model, smoking had little impact on lung cancer rates for the first 20 years of smoking, after which the effect of smoking increases dramatically. This model implies a reduced potency at higher smoking intensities like the pattern suggested in Refs. 14 and 15, where the departures from a linear pack-years effect were attributed to modifying effects of intensity and not duration.

There was a statistically significant time-dependent reduction (P < 0.006) in the ERR for those who reported that they had stopped smoking. The estimated decline for past smokers (relative to that for non-smokers of the same age) was approximately proportional to one over the square root of time since quitting. While the smoking ERR declines following smoking cessation (Figure 1A), lung cancer rates for past smokers never return to the level for non-smokers (Figure 1B). Although, for those smoking patterns, women have larger ERRs than men, the absolute rate estimates for male and female smokers are similar (Figure 1B).

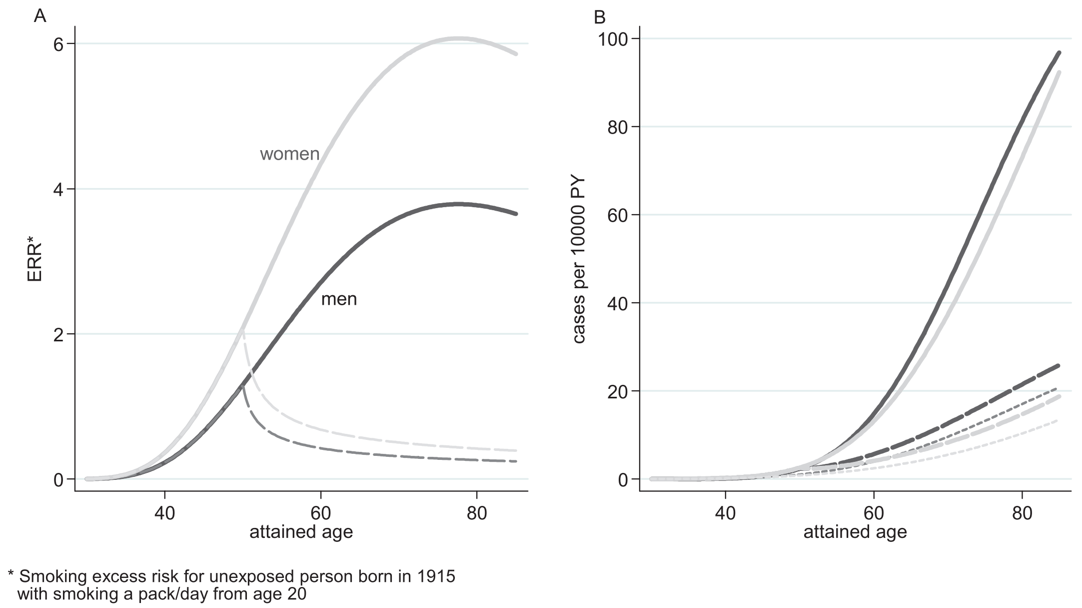


Figure 1. Gender-specific smoking effects on the excess relative risk (Panel A) and absolute rate (Panel B) as a function of age. The darker curves are for men and the lighter ones for women. The solid curves illustrate the modeled lung cancer risks for a person who smokes 20 cigarettes (one pack) per day from age 20. The long-dashed lines indicate the risk for an individual who stopped smoking at age 50. The short-dashed lines in Panel B indicate the risk for non-smokers. The curves correspond to risk for an unexposed person born in 1915.

Radiation effects and radiation by smoking interactions

Table 1B presents parameter estimates for radiation effects and their modifying effects, together with 95% CIs and information about the fit, from the ERR interaction models described earlier. The table also includes results from a model in which the radiation-effect parameters were estimated without allowance for smoking effects (radiation-only) as in most LSS reports.[3,16]

Both the deviance and AIC values suggest that the generalized-interaction models fit better than the simple interaction models and that the generalized multiplicative model described the data somewhat better than the generalized additive model. Models in which the generalized interaction was modeled in terms of pack-years or years smoked were also considered, but did not describe the data any better than the smoking-intensity models given in Table 1B.

Since most men smoke and most women do not, without allowance for smoking the estimated ERR/Gy for men was similar to that for a simple multiplicative model while that for women similar to that for a simple additive model. In all of the models except the simple additive model, the ERR/Gy was significantly larger for women than for men. The radiation-associated ERRs declined with increasing attained age while rising with increasing age at exposure (Figure 2).

There was no indication of statistically-significant curvature in the radiation dose response ($P > 0.5$) over the full dose range or when the data were restricted to the 0–2 Gy range ($P = 0.3$). Furthermore, the gender-averaged dose-response slope for the restricted range (0.67 per Gy) was similar to that for the full range (0.59). There were no indications of gender-dependence in effect modification by attained age ($P > 0.5$) or age at exposure ($P > 0.5$). Nor was there evidence of non-linearity for those effects ($P = 0.3$ for attained age and $P = 0.5$ for age at exposure).

Figure 3 illustrates how the ERR changes with smoking intensity and dose under three interaction models. The points in this figure are category-specific estimates from a generalized multiplicative model in which smoking-intensity categories replaced the linear-quadratic function of log intensity in the radiation model. The left panel describes the joint effect of radiation and smoking relative to the rates for non-smokers with no radiation exposure. The right panel describes the radiation effect in terms of the ERR/Gy relative to the risk for an unexposed individual with the same smoking history. The generalized interaction model suggests that at lower smoking intensities (10 cigarettes per day) the radiation effect tends to be greater than predicted by either the simple additive or multiplicative models, but that there is little or no apparent radiation effect for heavy-smokers (20 cigarettes per day). There was no indication that the risk pattern in the generalized interaction models depended on gender ($P > 0.5$).

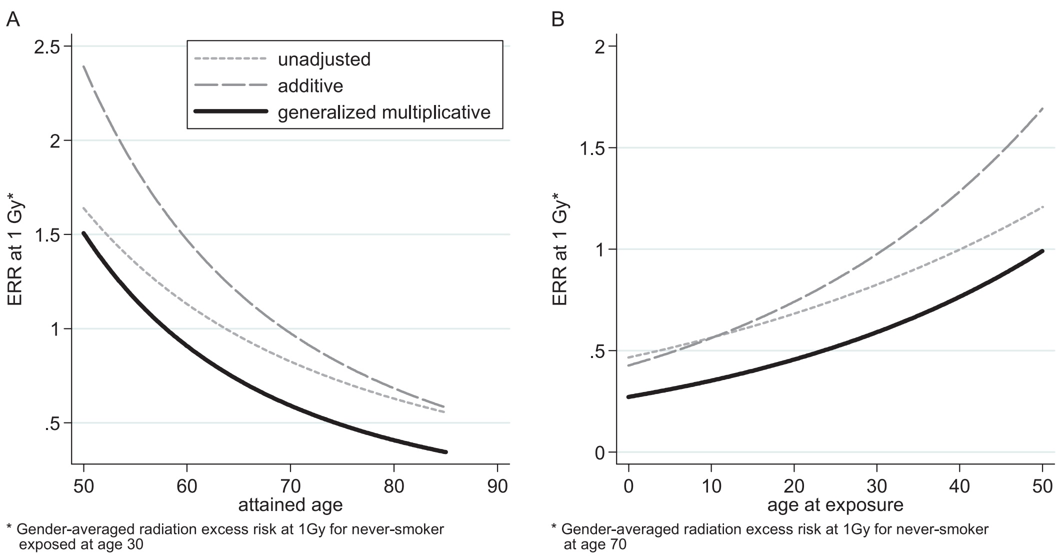


Figure 2. Effects of attained age (Panel A) and age at exposure (Panel B) on the excess relative risk (ERR) per Gy. The plots compare the gender-averaged risk estimates for three joint effect models. The generalized multiplicative model for non-smokers is indicated by the dark solid line while the additive model is indicated by the long-dashed line. For both of these models the ERR is relative to the risk for non-smokers. The short-dashed line is for a model with no adjustment for smoking. In this model the ERR is relative to the risk for an unexposed cohort member without regard to smoking status.

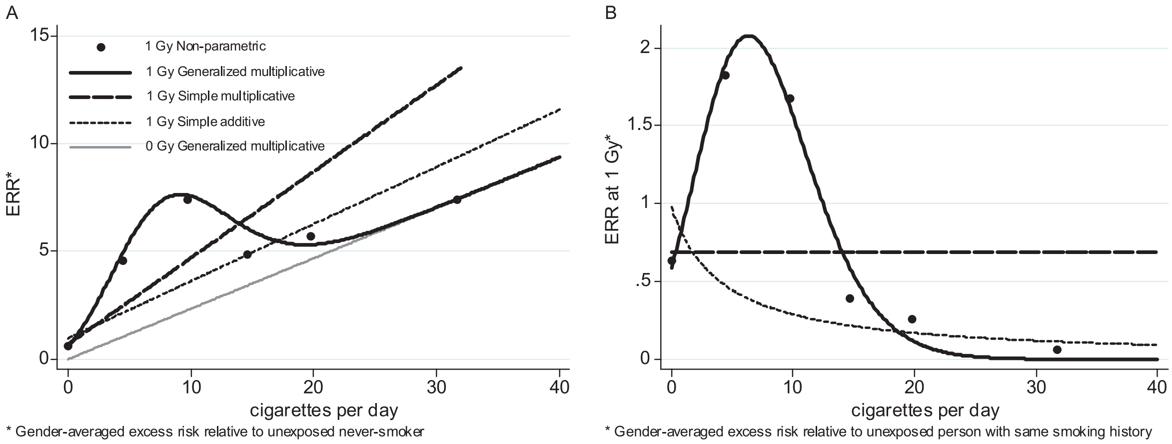


Figure 3. Variation of the excess relative risk (ERR) with smoking intensity. The gender-averaged risk estimates at age 70 following radiation exposure at age 30. Smoking was assumed to start at age 20 so that smoking duration was fixed at 50 years in this figure. Panel A describes the joint effect of radiation and smoking relative to the baseline rate for a non-exposed non-smoker. The thin long dashed line is the fitted ERR for a person with no radiation exposure. The solid line is the fitted ERR following exposure to 1 Gy under the generalized multiplicative model, the thick dashed line is the fitted risk under a simple multiplicative model, and the short-dashed line is the fitted ERR under a simple additive joint effect model. The points are based on a generalized multiplicative model in which smoking intensity categories replaced the linear-quadratic function of log intensity used in the generalized multiplicative model. Panel B presents radiation-associated excess risks for an exposure of 1 Gy relative to the risk of an unexposed person with the same smoking history.

Discussion

Questions about the joint effect of radiation and smoking are generally framed in terms of a choice between simple additive and multiplicative models. With additional follow-up, data from more cohort members, and more parsimonious description of the departures from simple models, we were able to reject both the simple additive and multiplicative models. Under our fitted generalized multiplicative model the joint effect appears to be super-multiplicative for light- to moderate-smokers (smoking less than a pack of cigarettes per day) but additive or even sub-additive for heavy-smokers (smoking a pack or more per day).

Adjustment for smoking can impact the modifying effects of gender and age factors on the radiation-related lung cancer risk. Our estimate of the ERR/Gy of 0.59 was smaller than that of 0.89 from the previous analysis by Pierce *et al.*[6] and that of 0.81 from the recent analysis of LSS lung cancer incidence with no adjustment for smoking.[3] The present estimate of the female:male ratio of ERR/Gy of 3.1 was smaller than that of 4.8 from the unadjusted analysis[3] but larger than smoking-adjusted estimate of 1.6 by Pierce *et al.*[6] For many types of solid cancers, the ERR/Gy decreases with increasing age at exposure,[3,16] but the unadjusted ERR/Gy for lung cancer has been found to increase with increasing age at exposure. Although it was suggested by Preston *et al.*[3] that this pattern might be a consequence of the failure to adjust for the effect of smoking, the current analyses indicate that this may not be the case. It may be that there is a certain pool of people genetically susceptible to lung cancer and that high levels of smoking have saturated that pool so that there is little room for an additional radiation effect. Another possible explanation is that radiation exposure prior to the start of smoking may be less harmful than radiation exposure after smoking initiation. In the LSS, age at exposure is highly correlated with whether or not radiation exposure occurred before or after smoking initiation, making it difficult to address this question. However, in an analysis in which the radiation effect was allowed to depend on whether or not one reported smoking before exposure, we found that radiation risks were not significantly higher for those who smoked before exposure and that the age-at-exposure effect became even more pronounced.

We estimated that smoking related relative risks were 4.6 for males and 6.8 for females who smoked a pack a day for 50 years. If the smoking duration and intensity were averaged over the general population, those values would be close to the risk estimates of 4.5 and 4.2 for male and female smokers, respectively, from another Japanese cohort study.[17] These values are much smaller than those reported from western populations,[18,19] which may in part reflect the higher lung cancer rates among non-smokers in Japan and other Asian countries than in the west. A recent study[20] suggested that lung cancer rates might be higher among Japanese non-smokers and relative risks lower among Japanese smokers, compared with the U.S. white counterparts. Our estimates of lung cancer rates for non-smokers were similar to those found for Japanese and Korean populations in an international comparison of lung cancer risks among non-smokers.[21]

Despite limitations which are discussed in the manuscript, we believe that this study provides the most comprehensive characterization of the joint effects of low-dose radiation and smoking on lung cancer in any radiation-exposed population. The results suggest that simple additive or multiplicative models may not adequately describe the complex interaction between smoking intensity and radiation and that a similar comprehensive analytical approach may be needed in risk estimation for smokers with medical or occupational radiation exposures. We think that further efforts should be made to develop methods for using generalized interaction models in radiation risk assessment. This study also is one of the most detailed quantitative analyses of smoking effects on lung cancer rates in a Japanese population, and whether or not the present findings are duplicated in other Japanese cohorts would be of interest as they have an important public health implication for one of the major cancer problems in Japan.

In summary, the gender-averaged ERR per Gy of lung cancer (at age 70 after radiation exposure at 30) was estimated as 0.59 (95% CI: 0.31–1.00) for non-smokers with a female:male ratio of 3.1. About one third of the lung cancer cases in this cohort were estimated to be attributable to smoking while about 7% were associated with radiation. The joint effect of smoking and radiation on lung cancer in the LSS is dependent on smoking intensity and is best described by the generalized interaction model rather than a simple additive or multiplicative model.

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Associations of Radiation Exposure and Circulatory Disease Mortality Risk Based on Hiroshima and Nagasaki A-bomb Survivor Data, 1950–2003*

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Introduction

Radiation effects on circulatory disease incidence or mortality have implications for public health, especially if there are effects at doses under 1 Gy. Given that the frequency of multiple computed tomography (CT) scans of the head or chest and of interventional radiographic procedures is increasing rapidly, information on whether these may confer risk for subsequent stroke or heart disease is important.

A number of studies, including randomized controlled trials, have documented that high doses of radiation to the heart from radiotherapy for Hodgkin disease or breast cancer cause an excess of heart disease deaths in later years,[1–4] and several studies have suggested that radiotherapy for Hodgkin disease,[5,6] childhood leukemia or brain tumors,[7] and head and neck cancer[8] increases the risk of stroke. There are also several suggestions that lower doses from occupational, medical, and environmental exposures may be associated with excess circulatory disease mortality,[9–14] although other studies do not find such low-dose effects.[15–19] Information on doses and potential confounding lifestyle factors is limited in many of the low-dose studies. In this paper published in the *British Medical Journal*, we examined the dose-response information on the risk of heart disease and stroke in the large Life Span Study (LSS) cohort of A-bomb survivors in Hiroshima and Nagasaki who have been followed up for 53 years, from 1950 to 2003.

Methods and Procedures

Study population

The LSS cohort defined on the basis of the Japanese national census in 1950 consists of 86,611 A-bomb survivors with estimated radiation doses. The LSS includes a large proportion of the survivors who were within 2.5 km of the hypocenters at the time of the bombings and still resided in Hiroshima or Nagasaki in 1950, plus a random age- and sex-matched sample of people 2.5 to 10 km from the hypocenter who sustained small to negligible radiation doses.[20] The study population was of all ages and both genders at the time of the bombings.

Individual doses have been carefully estimated using the recent improved DS02 dosimetry system, based primarily on their location and shielding at the time of the A-bomb.[21,22] Risks were estimated using weighted colon doses in gray (Gy) for all analyses.

The follow-up of vital status was conducted from 1 October 1950 to the end of 2003 and was based on the nationwide obligatory family registration system (*koseki*) that documents mortality and is virtually 100% complete. Causes of death were obtained from the official Vital Statistics Death Schedules based on the death certificates. Underlying and contributing causes of death were classified according to the International Classification of Diseases (ICD) version 7 (for deaths in 1950–1968), 8 (in 1969–1978), 9 (in 1979–1997), and 10 (in 1998–2003). However, for purposes of our analyses codes were converted to ICD 9 codes. Only underlying causes were used in the primary analyses.

Collection of covariate data and data from autopsy and tumor registry

A defined sub-cohort of 51,965 LSS members was sent a mail survey in 1978. Information was obtained from 36,468 (response rate of 70%) on sociodemographic (education, type of occupation), lifestyle (smoking, alcohol intake), and health variables (obesity, diabetes mellitus), which enabled the evaluation of possible confounding by these variables. Between 1950 and 1985, autopsy data were also available on over 1,900 deaths that had an underlying cause of circulatory disease on the death certificate, which permitted evaluation of diagnostic accuracy. To identify pre-existing cancer cases we used the Hiroshima and Nagasaki tumor registries (available since 1958) and tissue registries (since 1974).

Statistical analysis

The analyses were based on a summary of the number of deaths and person-years stratified by dose, city, sex, and five-year intervals of age at exposure, attained age, and follow-up period. Study subjects were divided into categories reflecting the number of study subjects at various weighted colon dose (in Gy = γ dose plus 10 times neutron dose).

Poisson regression methods for grouped survival data [23] were used to describe the dependence of risk on radiation dose and to evaluate the variation of the dose response with respect to city, sex, age at exposure, time since exposure, and attained age, essentially identical to the methods used previously to examine cancer mortality in this cohort.[20] Parameter estimation and tests were carried out with Epicure software,[24] and significance tests and 95% confidence intervals (CI) were based on likelihood profiles.

The primary models used here are excess relative risk (ERR) models of the form

$$\lambda_0(c,s,a,b)\left[1+ERR(d,e,s,a)\right]$$

where $\lambda_0(\cdot)$ is the baseline, or background death rate (i.e., the rate for people with zero dose) which depended on city (c), sex (s), attained age (a), and birth year (b). The function $ERR\ (d,e,s,a)$ describes the relative change in rates associated with dose d, allowing for the effects of sex, age at exposure (e) and attained age. Effect modifiers were examined using models corresponding to those in Preston *et al*.[20,25] Both dose and dose-squared terms were examined in order to evaluate the degree of linearity or curvature in the dose-response forms. A linear-threshold model was also tested. Differences in maximum likelihood or the Akaike Information Criterion (AIC)[26] were used to compare nested or non-nested models, respectively. A linear-threshold model was evaluated repeatedly for a wide range of possible values of a threshold dose (d_0) modeling the risk function ERR on doses d as $\beta(d - d_0)$ for $d > d_0$ or $d = 0$ for $d \le d_0$. The values yielding the maximum likelihood and 95% confidence bounds were empirically determined.

The impact of the possible confounding factors of smoking (never, past, present <20/day, present 20+/day), alcohol intake (regular, seldom/never), education (primary or less, secondary, college/university), occupation for household (professional/technical, clerical/sales, farmer/craftsman, transportation/service), obesity (body mass index [BMI] < 20, 20–25, 25+), and diabetes (yes/no) on the radiation risk estimates were examined, including codes for missing information. Cox-type regression models fitted to the individual data were included, where radiation dose was modeled as a linear ERR, and indicator variables for the potential confounders were included jointly in the models as conventional exponential relative risk terms by using the Peanuts program in Epicure.[24]

Results

There were 19,054 circulatory disease deaths among the 86,611 LSS members with DS02 dose.

Table 1. Number of subjects and deaths from circulatory disease

		Number of persons	Number of circulatory disease deaths	Number of stroke deaths	Number of heart disease deaths	Number of other circulatory disease deaths
Total		86,611	19,054	9,622	8,463	969
Gender						
	Male	35,687	7,607	3,958	3,261	388
	Female	50,924	11,447	5,664	5,202	581
Age at A-bomb exposure (years)						
	0–9	17,833	428	176	238	14
	10–19	17,563	951	404	508	39
	20–29	10,891	1,551	652	831	68
	30–49	25,774	9,712	4,735	4,575	402
	50+	14,550	6,412	3,655	2,311	446
Weighted colon dose (mGy)						
	<5	38,509	8,440	4,247	3,723	470
	5–	23,427	5,089	2,637	2,205	247
	50–	12,508	2,838	1,405	1,305	128
	200–	6,356	1,485	735	680	70
	500–	3,424	745	363	342	40
	1000–	1,763	341	176	158	7
	2000+	624	116	59	50	7

Table 1 shows the numbers of subjects and circulatory disease deaths by age, gender, and radiation dose. The table shows that the cohort has a wide range of doses but is weighted toward low doses, which indicates that it has considerable capability to examine low-dose risks and to examine the shape of the dose-response curve. There were 9,622 stroke deaths, 8,463 heart disease deaths, and 969 other circulatory disease deaths. The percent ERR per Gy (ERR/Gy) for all circulatory disease based on the linear model over the full dose range was 11% (95% CI: 5 to 17%; $p < 0.001$). That represents about 210 excess cases of circulatory disease mortality associated with the radiation exposure.

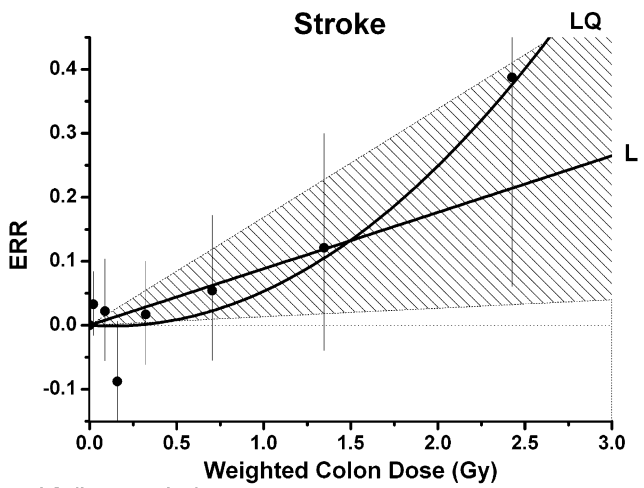
Stroke

The ERR/Gy for stroke based on the linear model over the full dose range was 9% (CI: 1 to 17%, p = 0.02) (Table 2). Figure 1 shows estimates of the shape of the dose-response for all stroke, including the fitted linear, pure quadratic, and linear-quadratic models. The test for non-linearity based on a comparison of linear and linear-quadratic dose-response models was not statistically significant (p = 0.17), but the pure quadratic model, which suggests there is relatively little risk at lower doses, nominally provided a slightly better fit than did the linear model (difference in AIC statistics of 1.87). This was confirmed by analyses of lower dose ranges, 0–1 Gy and 0–0.5 Gy, which showed ERR/Gy of 3% (CI: –10 to 16%) and –7% (CI: –28 to 16%), respectively. Figure 1 also shows that there was no apparent risk for the lower part of the dose range. There may be a non-negligible threshold below which there is no excess. The best estimate of a threshold dose was 0.5 Gy with an upper 95% confidence bound of about 2 Gy. However, the lower 95% confidence bound was not greater than 0, so there may be no threshold dose.

Table 2. Summary excess relative risks (ERR)[1] per Gy and excess additive risks[2] (EAR per 10^4 person-year Gy) for types of circulatory disease mortality [1]

	Indicated as underlying cause of death				Underlying or contributing cause of death	
	Deaths	p-value	% ERR/Gy (95% CI)	EAR/10^4 PY-Gy (95% CI)[2]	Deaths	% ERR/Gy (95% CI)
Total circulatory diseases	19,054	<0.001	11 (5 to 17)	5.5 (2.7 to 8.4)	25,113	15 (10 to 20)
Stroke	9,622	0.02	9 (1 to 17)	2.3 (0.4 to 4.4)	12,139	12 (5 to 19)
Heart disease	8,463	<0.001	14 (6 to 23)	3.2 (1.3 to 5.2)	14,018	18 (11 to 25)
Other circulatory disease	969	>0.5	2 (–18 to 29)	0.1 (–0.4 to 0.7)	5,846	58 (45 to 72)

[1] Estimates are based on a linear model, adjusting for city, gender, age at exposure, and attained age.
[2] The average EARs are calculated directly from the fitted ERR models.



L: linear, LQ: linear-quadratic

Figure 1. Radiation dose-response (ERR) for stroke mortality, showing the linear and linear-quadratic functions. The shaded area is the 95% confidence region for the fitted linear line. The vertical lines are 95% confidence intervals for specific dose-category risks. Point estimates of the risk for each dose-category are indicated by circles.

An analysis of effect modification of stroke risk by gender, attained age, and age at exposure showed a statistically significant difference for attained age ($p = 0.04$); the radiation ERR/Gy for stroke was higher before age 60 than after, especially among men. There also was a nonsignificant indication ($p = 0.23$) that the radiation risk of stroke may be highest after exposure at young ages.

Heart disease

The risk estimate for all heart disease based on the linear model in the full dose range was 14% ERR/Gy (CI: 6 to 23%, $p < 0.001$) (Table 2). Results for the linear, linear-quadratic and pure quadratic models are shown in Figure 2. The test for non-linearity based on a comparison of linear and linear-quadratic dose-response models was not statistically significant ($p > 0.5$). A pure linear model fits the data nominally better than a pure dose-squared model (difference in AIC statistics of 2.47). The ERRs for heart disease over restricted dose ranges were similar to that for the full dose range. Specifically, the ERRs/Gy based on the linear model for the dose ranges under 2, 1, and 0.5 Gy were 14% (CI: 4 to 25), 18% (CI: 3 to 33), and 20% (CI: –5 to 45), respectively. In Figure 2 the slope over the lower part of the dose range was almost identical to the one for the entire dose range. The best estimate of threshold dose was 0 Gy with an upper 95% confidence bound of about 0.5 Gy. There was no significant effect modification by gender, age at exposure, or age at risk.

Confounding factors and misdiagnosis

The impact of the possible confounding factors on the radiation risk estimates was examined among the 51,965 LSS subjects in the 1978 mail survey and we found that the association between radiation and circulatory disease was unlikely to be an artifact of confounding (see manuscript).

We also examined the diagnostic accuracy of death certificates by comparing them with autopsy reports among the 1,963 death-certificate designated circulatory disease cases for whom autopsies were available from our autopsy program between 1950 and 1985.[27] The accuracy of the diagnoses on the death certificate (DC) is fairly good for stroke and heart disease, though the accuracy of the DC was decreased for finer sub-categories (see manuscript).

Circulatory disease deaths based on death certificates may include misdiagnosed cancer deaths or cases arising from cardiotoxicity due to cancer chemotherapy or radiotherapy. To remove the effects of cancer misdiagnosis, risks were estimated after excluding persons who had previous cancer diagnoses, based on our tumor registry data. The ERRs excluding pre-existing cancer diagnoses were reduced, but the dose responses remained sgnificant (see manuscript).

Although the designated underlying cause was used in the mortality analyses, it is difficult to select a single cause of death when several correlated diseases or conditions are contributing to death. Therefore, the risks were examined based on both underlying and contributing causes of death (Table 2). The radiation-dose responses were nominally higher than those based on underlying cause of death alone (12% vs. 9% ERR/Gy for stroke, respectively, and 18% vs. 14% for heart disease), which lends additional support to the hypothesis of radiation risk.

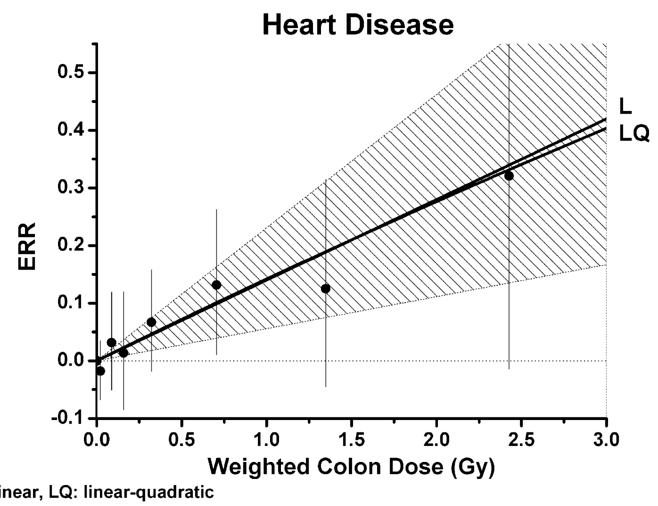


Figure 2. Radiation dose-response (ERR) for heart disease mortality, showing the linear and linear-quadratic functions. The shaded area is the 95% confidence region for the fitted linear line. The vertical lines are 95% confidence intervals for specific dose-category risks. Point estimates of the risk for each dose-category are indicated by circles.

Discussion

The present study reports dose-response evidence for heart disease and stroke among A-bomb survivors over the dose range 0–4 Gy (mostly 0–2 Gy) based on well-characterized individual doses and essentially complete mortality ascertainment over the period of 5 to 58 years after radiation exposure. This report updates earlier brief reports of a dose-related circulatory disease excess among A-bomb survivors.[20,28,29] The present results, based on ~25% more deaths than the previous paper, are substantially stronger, and more elaboration of the associations is now provided.

As shown in Table 1, at the youngest ages of exposure (more recent birth cohorts) the heart disease deaths outnumber those due to stroke, whereas the opposite is true of the earlier birth cohorts; this reflects the general secular trends in the Japanese population. The table also shows that the cohort has a wide range of doses but is weighted toward low doses, which indicates that it has substantial capability to examine low-dose risks and to examine the shape of the dose-response curve.

Though the present data were statistically consistent with linearity over the full dose range in this study, there is considerable uncertainty about the shape of the dose response in the low-dose range. The extent of curvature seemed to be larger for stroke than for heart disease; a pure dose-squared model fits the stroke data slightly better than a pure linear model, whereas the linear model provided a better fit for heart disease. However, the dose response was not statistically significant for either endpoint when the calculation was limited to the dose range 0 to 0.5 Gy, implying that evidence regarding risk below about 0.5 Gy is limited. For stroke, the estimated threshold dose was 0.5 Gy with an upper 95% confidence bound of about 2 Gy. For heart disease, the estimated threshold dose was 0 Gy with an upper 95% confidence bound of about 0.5 Gy.

Additional analyses supported the association of radiation with stroke and heart disease. Adjustment of the data for other potential risk factors for circulatory disease—obesity, diabetes, smoking, alcohol consumption, education, and occupation—had almost no impact on the radiation associations, while an analysis for possible misdiagnosis of cancer as circulatory disease showed a small diminution of radiation risk. Because underlying cause of death is often uncertain, analyses of stroke and heart disease as either an underlying or contributing cause were also performed and showed even nominally stronger associations with radiation than the analyses of underlying cause alone.

The findings of the epidemiologic study of circulatory disease among A-bomb survivors are confirmed and extended by our Adult Health Study (AHS), which consists of biennial clinical and laboratory examinations since 1958 of about 15% of the LSS cohort members. The AHS has found dose-related increases in the incidence of stroke and myocardial infarction,[30,31] and in the incidence or prevalence of hypertension,[30,32,33] elevated serum cholesterol levels,[34] and aortic arch calcification.[35] Late radiation effects also have been found for potential biomarker precursors of circulatory disease, including biomarkers for inflammation,[36–38] deficient immunological responses,[39] and alterations in immune cell repertoire.[40,41] Despite the limitations of our studies (discussed in the manuscript), the findings present a reasonably coherent picture of preclinical and clinical risk of circulatory disease associated with radiation exposure. However, this needs to be complemented by low-dose risk assessment based on mechanistic and animal models.

Although epidemiological and experimental data are limited, a number of studies suggest the possibility of radiation effects on circulatory disease. Among medically exposed cohorts, excess heart disease mortality has been demonstrated among patients who received radiotherapy for Hodgkin lymphoma or breast cancer (e.g., Refs. 1–4, 42). At somewhat lower doses, an increase in coronary heart disease was observed among patients who received radiotherapy for peptic ulcer.[9] An association was also seen among scoliosis patients who received multiple fluoroscopic examinations,[43] but not among tuberculosis (TB) patients who received multiple chest fluoroscopic examinations[16] nor among patients who received X-ray treatment for benign gynecologic disease.[44,45]

Studies of cohorts with occupational or environmental radiation exposure have not provided clear evidence for or against a radiation-associated increase in circulatory disease mortality.

Most of those studies were not able to adjust for potential lifestyle or other confounding factors, and some of the studies had no or only crude individual dose estimates. Most of the low-dose studies had limited statistical power and some potential for biases; consequently the potential for both false-positive and false-negative results may be high. The United Nations Scientific Committee on the Effects of Atomic Bomb Radiation (UNSCEAR) concluded there is little evidence, other than the atomic bomb studies, to support an association between circulatory disease and radiation in the dose range less than 1–2 Gy.[46]

Conclusions and Implications

The effect of radiation on circulatory disease risk is potentially a very important public health issue. Given the widespread use of multiple CT scans[47,48] and other relatively high-dose diagnostic medical procedures, as well as radiotherapy that exposes the heart, the implications are substantial insofar as there are effects at doses under 1 Gy. The potential magnitude of the risk is shown by the fact that, in the LSS cohort who received whole-body irradiation, the radiation-related excess of circulatory disease deaths (~210) is about one third as large as the total excess number of cancer deaths (~625).

The study provides the strongest evidence available to date that radiation may increase the rates of stroke and heart disease at moderate dose levels (mainly 0.5–2 Gy), but there is a need for robust confirmatory evidence from other studies. While the present results below 0.5 Gy are not statistically significant, the additional cases occurring with further follow-up time should provide more precise estimates of the risk at low doses.

[The authors would like to thank the members of the RERF Master File Section for their diligent efforts to provide accurate data on mortality in the LSS, and Hiroshima and Nagasaki tumor and tissue registries for their approval for the use of the data. We also thank Yoshisuke Nonaka for his statistical advice.]

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Recollections of Japan

William J. Schull, Former Vice Chairmam

[Editors' note: RERF staff were fortunate last May to have a visit from Dr. William Schull who has been one of our most avid supporters and who has served ABCC and RERF in several capacities, including Permanent Director. He spent a few days at RERF and on May 21 gave a lecture entitled "ABCC in the Olden Days." "Jack" has promised to write up his informative and entertaining lecture for a future issue of *Update*, but for now has submitted a short human interest note.]

As a child, and that was many, many years ago, I was repeatedly told by my parents that to enjoy life to its fullest I should never take myself too seriously. Yes, I needed to be focussed and study hard, but it was a mistake to believe that the world would see me as a new Messiah. Their advice has brought me a myriad of happy memories of my life in Japan. But occasionally there was a sad memory or an especially funny one. It is a funny, but embarrassing one about which I write now.

For years, ABCC and subsequently the Radiation Effects Research Foundation has maintained a travel office to expedite and assist in travel. The head of that office, until a few years ago, was Jimmy Yorioka, who died recently. Yorioka-san was also the head of the library, and as such was well-informed on travel. It was through him that I learned that employees of the Ministry of Health, Labour and Welfare (MHLW) when they traveled could stay at the various accommodations maintained by the Ministry. Perhaps the best known of those places are the numerous Kosei Nenkin Kaikans. Those hotels or inns are reasonably priced, generally attractive, well maintained, and have their own dining facilities. As a result, when we traveled within Japan, Jimmy would try to book rooms for us at one of the MHLW facilities.

The incident of which I write occurred in 1986 when my wife's youngest sister, Mary Jane, and her husband, James Mintner, visited us in Japan. At the time I was one of the Foundation's "permanent" directors and lived in Hijiyama Hall. Naturally we were anxious for them to see as much of Japan as possible in their brief stay. I had a car which meant that we could visit any place that was reasonably accessible by car from Hiroshima without much prior arrangement. One such place was Izumo. Given the importance of Izumo's great shrine and the shrine's beauty, we thought it important to arrange a trip there. Jimmy was able to book us two double rooms at the Ministry's facility in Izumo. Once we learned that we had reservations, late on a Friday afternoon, we drove across Honshu until we reached national highway 3 where we turned south to Izumo (actually mostly west). The Kaikan was expecting us and had set aside two comfortable rooms. The next day, that was Saturday, we toured the shrine and drove out to Misaki and the Japan seaside. I do not recall where we ate, but the food must have been good or I would undoubtedly have remembered otherwise. On Sunday morning, we intended to leave the hotel early, drive on west along the coast to Hagi, and then turn back across Honshu to Tsuwano and ultimately Hiroshima. I tried to impress on everyone that this was a lot of travel, many places to see, and that we should leave the hotel promptly the next morning.

Dr. William J. Schull when he visited RERF in May 2010

Since I had been as adamant as I had, when Sunday broke I was up early and presented myself to the Kaikan's front desk to check us out and to pay the bill. After I said what I thought was intelligible Japanese, "Kanjo kudasai (please bring the bill)," the clerk asked me to please wait for the hotel's nurse had not yet come. This seemed to me to be a very strange request, but I sat down to await the arrival of the nurse. However, as the moments passed, and more and more guests checked out, I became concerned. Finally, I thought I should go back to the front desk and attempt to understand why I seemed to be treated differently from other guests. This time I again repeated the same request, or so I thought, and was immediately presented with the bill. I happily paid this but remained perplexed. It was much later that I learned the word for an enema is kancho. Apparently the first clerk had thought that I wanted an enema and the only one who could administer such was the hotel nurse.

In Memoriam

Yutaka Hosoda


Dr. Yutaka Hosoda in 1985

Dr. Yutaka Hosoda, who served as Chief of the Clinical Studies Department during the four-year period starting in 1985 and was one of the research scientists for whom I had the greatest esteem, passed away at the age of 84 on October 3, 2010, surrounded by family at his own home. I was very shocked at this sad news, because I had heard of his bad health only two days before by chance and intended to visit him at my next opportunity to travel to Tokyo.

Dr. Hosoda worked for the Radiation Effects Research Foundation for five short years, including his tenure as Department Chief, but he transformed the Department of Clinical Studies from one of conducting only health examinations to a true research department. Prior to coming to RERF, Dr. Hosoda served at the Japan National Railways Central Health Institute for many years, working on epidemiological research activities with a focus on such thoracic diseases as sarcoidosis and pneumoconiosis. At the Department of Clinical Studies, Dr. Hosoda instructed us in epidemiological research, making good use of his work experience. He introduced us to distinguished researchers throughout the country and helped us increase the range of our research activities. Several studies, including the first longitudinal analysis of disease incidence in the Adult Health Study and non-cancer studies, commenced under Dr. Hosoda's direction. Despite his gentle nature, Dr. Hosoda maintained a forceful attitude of working to develop the strengths of each individual research scientist and criticizing the faults that needed to be changed. It seems like just yesterday that, when I made an excuse for not being able to do something, Dr. Hosoda upbraided me in a quiet tone. "Don't justify why you can't do something; instead find out how you can," he said. I learned so much from him, including the importance of a proactive attitude and gracious treatment of staff, among other things. I feel extraordinarily fortunate that I met Dr. Hosoda when young.

Dr. Hosoda's funeral was held in line with his last will and testament: only a cross was placed on the altar, slightly more flowers than normal decorated the worship services, and funeral attendants were requested to inscribe their farewell messages on his white wooden casket. I wrote "Thank you" on the casket and meant it from the bottom of my heart. Please continue to watch over me now from heaven, Dr. Hosoda. I pray for the repose of your soul.

(by Saeko Fujiwara, Chief, Department of Clinical Studies, Hiroshima)

Elaine Ron

It was sad news when we learned that long-time friend and supporter of the RERF research community, Dr. Elaine Ron, lost her battle with cancer Friday, November 19, one day after her 67th birthday. The Chief of the Radiation Epidemiology Branch (REB) of the U.S. National Cancer Institute's (NCI) Division of Cancer Epidemiology and Genetics (DCEG), Dr. Martha Linet, reported that Dr. Ron died peacefully at her home with her son Ariel holding her hand. Dr. Ron and her son lived in Hiroshima from August 30, 1990 until August 22, 1991 when Elaine was a Research Associate in the Department of Epidemiology. She continued her close and long-term relationship with and support of RERF as an Expert Advisor to the Department of Epidemiology, and she visited RERF to collaborate with our scientists. She was instrumental in establishing the long-term contract between the NCI, the National Academy of Sciences, and RERF, which has resulted in numerous publications. For example, Dr. Ron played a key role in the 2007 solid cancer incidence manuscript working closely with RERF scientists and colleagues Dale Preston, Shoji Tokuoka, Sachiyo Funamoto, Nobuo Nishi, Midori Soda, Kiyohiko Mabuchi, and Kazunori Kodama.

Dr. Ron first joined the NCI in 1986 and served as Chief of the REB from 1997 to 2002. The Director of the DCEG, Dr. Joseph F. Fraumeni, Jr., pointed out that Dr. Ron "was an internationally renowned


Dr. Elaine Ron in 1990

expert in the health effects of exposure to radiation, including medical, occupational, and environmental settings. Her earliest work on the effects of treatment for tinea capitis in Israel is considered a groundbreaking classic." He went on to mention that at a recent NCI Board of Scientific Councilors' review of the REB, the site visitors "praised Elaine's work as being of the highest quality and having significant impact on public health and radiation policy." They also commented on her exceptional mentoring, collegiality, and senior leadership in the Branch and Division. Dr. Fraumeni added that "Elaine had great warmth, humor, and forthrightness, with a passion to fight injustice, and will be deeply missed."

Dr. Ron served on many expert radiation committees including Committee 1 of the International Commission on Radiological Protection. At the time of her death she was serving on the Radiation Effects Research Foundation Recruitment Committee for the National Academy of Sciences' Nuclear and Radiation Studies Board. Dr. Ron has been commended for her exceptional mentoring by recipients of Gilbert Beebe Fellowships—a program she strongly supported—and by RERF scientists who have spent time training at the NCI such as Drs. Kyoji Furukawa and Ritsu Sakata. RERF's Chief of Research Dr. Roy Shore responded to the sad news by pointing out that "Dr. Ron had such vitality and humaneness." The RERF community has lost a colleague, a strong supporter, and a friend.

(by Evan B. Douple, Associate Chief of Research)

[Editors' note: As this issue of *Update* goes to press, we were saddened to learn of the deaths of Dr. Tsutomu Sugahara, former RERF director and scientific councilor, and Ms. Louise Cavagnaro, the first director of the ABCC nursing staff.]

2010 Open House in Hiroshima and Nagasaki

August 5 and 6 and August 8 and 9, RERF held its annual Open House in Hiroshima (16th annual event) and Nagasaki (14th annual event), respectively. The theme was "Forefront of radiation and health sciences," and included this year was a special exhibition titled "Forefront of high-precision radiotherapy." The Open House also featured a special panel-based exhibit introducing the activities of the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE). An artistic exhibit titled "Kage-e (shadow picture) exhibition of small prayers from Hiroshima" (see photo) attracted the attention of visitors for its unique concept.

In the event's lectures, which have become part of the regular program in Hiroshima, Dr. Asao Noda, Chief, Cytogenetics Laboratory, Department of Genetics, and Dr. Kotaro Ozasa, Chief of the Department of Epidemiology, spoke about "What is radiation?" on the 5th and "What is radiation epidemiology?" on the 6th, respectively, with both lectures attended by large enthusiastic audiences. The Hiroshima Laboratory's Open House drew 1,476 visitors for the two days—the largest number in the event's history. Could it have been due in part to the eye-catching "PR bus masks" on the front of Hiroshima buses (see photo)?

Dr. Masataka Taga and Dr. Kiyohiro Hamatani, from RERF's Cell Biology Laboratory in Hiroshima's Department of Radiobiology/Molecular Epidemiology, traveled to Nagasaki and provided explanations in a readily understandable manner. Also, Dr. Kotaro Ozasa, Chief of the Hiroshima Department of Epidemiology, together with Drs. Akihiko Suyama and Midori Soda and the staff at the Nagasaki Department of Epidemiology, provided explanations regarding the A-bomb survivors' mortality study and cancer registries to the visitors in Nagasaki.

As in past years, the examination "corners" in RERF Nagasaki for testing arteriosclerosis and other such conditions presented by the Department of Clinical Studies were very well received by adult visitors. The children corners featuring an experiment in instantaneous freezing of flowers and microscopic observation of cells collected from the mouths of visitors themselves also proved to be very popular. The Nagasaki Laboratory's Open House attracted 515 visitors for the two days.

"Kage-e exhibition of small prayers from Hiroshima"

A city bus with a mask for Open House advertisement

Research Protocols Approved in April–September 2010

RP 4-10 Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors

Ohishi W, Fujiwara S, Akahoshi M, Suyama A, Kasagi F, Furukawa K, Hsu WL, Takahashi N, Satoh Y, Kusunoki Y, Yamada M, Neriishi K, Tatsukawa Y, Takahashi I, Hida A, Imaizumi M, Sera N, Grant EJ, Ozasa K, Cologne JB, Cullings HM, Kodama Y, Katayama H, Watanabe T, Nakamura N

Rationale: The heritable effects of exposure to ionizing radiation have long been a public health concern. However, there are no human data on the potential risk of adult-onset multifactorial diseases in the offspring of exposed persons. This longitudinal clinical study of the F_1 offspring of A-bomb survivors will provide the first information on this important issue.

Objectives: The objectives of the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors (F_1 Clinical Study) are (1) to elucidate the effects of parental exposure to A-bomb radiation on the development of multifactorial diseases and subclinical conditions among the F_1 offspring of A-bomb survivors, (2) to increase the precision and reliability of risk assessments, (3) to preserve biological samples for future research studies, and (4) to contribute to the health and welfare of the F_1 population via health examinations and health guidance.

Methods: This prospective study will conduct periodic health examinations of a fixed cohort of F_1 offspring born to A-bomb survivors between 1946 and 1984. In the initial F_1 health effects study, 14,175 people indicated they were potentially willing to undergo health examinations among the 16,789 subjects of mail surveys who responded to questionnaires concerning health and living habit by mail or telephone between May 2000 and November 2008. Of those, 11,984 actually attended the Radiation Effects Research Foundation (RERF) clinic for an examination by the end of November 2008. After excluding 397 of the 14,175 because of subsequent death or contact refusal and 1,320 with currently unknown addresses, a total of 12,458 are potentially eligible.

The F_1 Clinical Study with health examinations will be carried out every four years. First, brochures of the health examination will be sent to all subjects, and secondly, participation in a clinical study will be requested by telephone. A letter explaining the health examination and samples of informed consent forms will be sent in advance to those who express a desire to participate in the health examination. In the F_1 Clinical Study, upon obtaining informed consent from the participant, the health examination will include a sociodemographic, lifestyle and medical-history interview, physical examination, anthropometric measurements, blood pressure measurements, electrocardiogram (ECG), urinalysis, blood/biochemical tests, stool occult blood test, abdominal ultrasonography, chest X-ray examination, and so on. Multifactorial diseases such as hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, and stroke detected via these examinations will be analyzed in relation to radiation exposure of the parents of the F_1, taking into consideration confounding factors. Blood and urine taken from those who gave their consent will be preserved for future research studies.

The F_1 Clinical Study will contribute to the health management and welfare of the F_1 offspring of A-bomb survivors by feeding back the results of the health examination, providing appropriate health guidance, and providing an outside medical referral if necessary.

The procedures and contents of the health examination, the ethical issues, data management, and so on are generally similar to the previous F_1 Clinical Study (FOCS). Future research studies using stored biological samples will be conducted after a separate detailed research protocol is prepared and approved by the usual RERF procedures.

RP 5-10 Analyses of Molecular Characteristics of Colorectal Cancer among Atomic-bomb Survivors

Ito R, Hamatani K, Taga M, Imai K, Kasagi F, Ozasa K, Katayama H, Cologne JB, Misumi M, Izumi S, Oue N, Yasui W, Nakachi K, Kusunoki Y

Certain solid cancers show a significant and relatively high excess relative risk (ERR) from radiation exposure in the Life Span Study (LSS) of atomic-bomb (A-bomb) survivors. Those victims who had A-bomb exposure at a young age (0–19 years old) show a higher ERR of solid cancers, even 60 years after exposure, than do those exposed at over 20 years of age. Pathological studies have in the past provided significant information about the histological characteristics of various solid cancers that developed among A-bomb survivors, some of which seem to differ from those in the non-exposed population.

Although little has been proved about the molecular characteristics of solid cancers among A-bomb survivors, preliminary results obtained from our pilot study on colon and rectal cancers among A-bomb survivors implied that prior atomic radiation exposure might influence microsatellite instability (MSI) status and result in an increase in the relative frequency of MSI-high (MSI-H) colon cancer. In addition, MSI-related molecular events, typically genetic and epigenetic alterations of the *MLH1* and Ras-signaling related genes, might also be influenced by radiation exposure. Determination of colon and rectal cancers with MSI or chromosomal instability

(CIN) is an important issue that forms the basis of this study. MSI status will be examined by DNA fragment analysis using six different microsatellite markers. In addition, CIN status will be examined by analysis of gain or loss of CIN-related chromosome loci with real-time polymerase chain reaction (PCR) or the PCR-restriction fragment length polymorphism (PCR-RFLP) method using single nucleotide polymorphism (SNP) loci, respectively.

Based on findings obtained from the pilot study, we propose the following hypothesis: The carcinogenic pathway with MSI may preferentially occur in colon cancer, but not in rectal cancer, among A-bomb survivors. To test this hypothesis, the following questions will be clarified by examination of about 140 cases with colon or rectal cancers including 20 subjects exposed to high radiation dose: 1) Whether radiation exposure has a stronger relationship with MSI-H colon cancer than with microsatellite stable/MSI-low (MSS/MSI-L) colon cancer or overall rectal cancer; 2) If this is the case, is radiation exposure associated with the occurrence of genetic and epigenetic alterations, specifically methylation of MSI-related genes (DNA repair genes, Ras-signaling-related genes, CpG island methylator phenotype [CIMP]-related genes) in colon cancer?; 3) Whether radiation exposure is associated with CIN-positive colon and rectal cancers; 4) If answer to question 3) is yes, whether radiation exposure influences the most important initial event (i.e., *adenomatous polyposis coli* [*APC*] gene alteration) or subsequent events; and 5) Are there any differences in pathological parameters (e.g., differentiation, development, progression, and host immune reaction to cancer) between non-exposed and exposed MSI- or CIN-positive colon and rectal cancers?

In this study, we will examine those questions in the order of descending priorities indicated by the item numbers 1) to 5).

RP 6-10 Intrinsic Subtypes of Breast Cancer among Atomic-bomb Survivors (Addendum to RP 5-08)

Yonehara S, Nishisaka T, Nakashima M, Sekine I, Tokuoka S, Soda M, Suyama A, Furukawa K, Hirai Y, Nakamura N, Yang R, Mabuchi K, Ozasa K

'Intrinsic' subtypes of breast cancer defined by gene expression profiling studies are thought to be associated with pathogenesis and prognosis (biological properties) of breast cancer, and seem to be related to some etiologic factors. This molecular classification can be approximated by immunohistochemical (IHC) staining of key markers. As part of the special cancer incidence study (RERF RP 5-08: Breast Cancer Incidence among Atomic-bomb Survivors, 1950–2005), we propose to investigate the IHC subtypes of breast cancer cases to add new insights into biological properties of breast cancer in relation to atomic-bomb radiation exposure. Collaborating with pathologists and hospitals in Hiroshima and Nagasaki, we will collect paraffin-embedded tissues of breast cancers that occurred in the members of the Life Span Study (LSS) population, and perform IHC staining of targeted receptor markers to study associations of specific subtypes and radiation exposure with consideration of patient's age and calendar year at diagnosis, birth cohort of the subjects, age at exposure to radiation, and also anthropometric indices, reproductive histories, and other individual factors. The results will provide insights into biological mechanisms of radiation-induced breast carcinogenesis and provide important information for future molecular studies of radiation-related subgroups to elucidate possible molecular changes associated with radiation-induced breast cancer.

RP 7-10 Study of Body Composition of the Hiroshima Adult Health Study Population

Tatsukawa Y, Fujiwara S, Harris TB, Misumi M, Ohishi W, Masunari N, Yamada M, Oyama H, Kasagi F

Background: Some recent results from studies of atomic-bomb (A-bomb) survivors have shown a positive association between radiation dose and incidence of arteriosclerotic diseases such as hypertension and myocardial infarction (MI). The underlying mechanisms of radiation dose effects on arteriosclerotic diseases, however, remain elusive. In addition, there are limited numbers of reports on the presence or absence of racial differences in the health effects of body composition.

Objectives: The objectives of this prospective study include: 1) testing whether radiation exposure is related to increased incidence of arteriosclerotic diseases and their risk factors through modifications in body composition; 2) examining effects of body composition modifications, particularly aging-related loss of muscle mass (sarcopenia), on the health of the Japanese people, such as the prevalence and incidence of arteriosclerotic diseases, and associated risk factors and mortality; and 3) comparing Hiroshima Adult Health Study (AHS) participants and U.S. Health, Aging, and Body Composition (ABC) study participants, with respect to potential racial differences in health effects associated with body composition (international collaborative study).

Methods: Study subjects will total approximately 2,200 Hiroshima AHS participants who underwent whole-body composition examination by dual energy X-ray absorptiometry (DEXA) during the period 1994–1996. In the Hiroshima AHS, measurements of whole-body/regional (trunk, limb, etc.) fat mass, lean mass, and bone mineral content (BMC) were conducted by DEXA starting in 1994. Those data are already stored in a database and available for use. In this prospective study, we will examine relationships between DEXA-based body composition and radiation dose, and the prevalence and incidence of arteriosclerotic diseases plus associated risk factors and mortality. Mortality endpoints will include all causes, ischemic heart disease, stroke, and possibly other cardiovascular diseases, if feasible.

This study may be useful to elucidate mechanisms of the relationship of radiation dose to arteriosclerotic diseases and their risk factors. Furthermore, the international collaborative study should be meaningful for both the A-bomb survivors and the general Japanese population.

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Publication Using RERF Data

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

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