放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
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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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Editorial Policy

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From the Editors

Welcome to *RERF Update*!

As efforts continue to try to bring the three Fukushima power plants to cool down nine months after the accident, RERF continues to provide information and assistance in many forms to the citizens of Japan and the rest of the world. The A-bomb survivors of Hiroshima and Nagasaki should be recognized for their enormous contributions to the ABCC and RERF's search for knowledge and understanding of the risks of exposure to radiation. The results of those studies are now being applied to serve decision-making and the citizens of the survivors' own homeland, Japan, during this period of considerable uncertainty, misinformation, and misunderstanding. In this issue we begin by providing a brief summary of RERF scientists' responses, contributions, and involvement as the planning for follow-up studies of those affected in the Tohoku region of northern Japan continues. A public lecture series reporting and explaining the findings of RERF that was begun last year in Hiroshima, has now been begun in Nagasaki (see cover photo). The second of the public lectures was held in Hiroshima on December 10 and included "Thinking about low-dose radiation exposure risk" and "Methods for radiation dose assessment." In Facts and Figures you will also get a sense of the many contacts that have been made requesting information from RERF's website.

The Fukushima accident has impacted RERF in many ways. One side effect has been that several distinguished scientists from around the world have visited RERF as part of their consultative work in Japan, some of them for the first time. For example, please read about the visit of Dr. Daud Mohamad, Deputy Director General and Head of Nuclear Sciences and Applications of the International Atomic Energy Agency (IAEA) who was also accompanied by Dr. Eduardo Rosenblatt, Head of the Applied Radiation Biology and Radiotherapy Section of the IAEA.

IAEA Deputy Director General Daud Mohamad (second from right) and Dr. Eduardo Rosenblatt (right) being briefed by the directors and senior staff of RERF on November 22

Please read about the first meeting of the Board of Councilors (formerly the Board of Directors) under the new guidelines required as RERF transitions to a public-interest incorporated foundation (PIIF). And finally, summaries of three recent RERF research papers were selected for a number of reasons. Two of the authors, Drs. Asao Noda and Waka Ohishi, were recently promoted to Assistant Department Chiefs in their respective departments. Dr. Noda is planning an international workshop in January that will focus on the role of stem cell research in radiation carcinogenesis and in this issue he describes an interesting model that he has developed in his laboratory. The papers of Dr. Ohishi and Dr. Ikuno Takahashi represent examples of the use of RERF's clinical databases to study risks of diseases associated with an aging population. Such studies were the focus of a visit by Dr. Judith A. Salerno, Executive Officer of the Institute of Medicine of the National Academies. Dr. Salerno was formerly Deputy Director of the U.S. National Institute on Aging (NIA) and she participated in a small workshop with RERF scientists to discuss how RERF's research might contribute to the study of aging. Such research is important since it improves our understanding of the background risks from "natural diseases" and thereby improves the quality of our radiation risk estimates. The knowledge gained also benefits the health of the A-bomb survivors and medicine for all mankind—sounds very consistent with the mission of RERF and the requirements of a PIIF too!

We hope that you enjoy this issue and don't hesitate to let us know how we might improve our reporting of RERF's many activities. Mata oidekudasai (goodbye and please come again),

Evan B. Douple
Editor-in-Chief

Yuko Ikawa
Technical Editor

Letters to the Editors

As to the article on nursing in the years of ABCC (*RERF Update* Volume 20, Issue 2, 2009), I found it very interesting; however, there is one significant error. Chiye (Chiyoko) Watanabe was not the second director of nursing. The head of nursing after Louise Cavagnaro left would have been Mildred Sherwood and she shared that function with Marion Batchelder. In fact, these are two of the "gaijin" women in the center of the front row of the picture of the nurses that accompanied the article. In this same picture, Chiye Watanabe is the second person on the left in the front row. Chiye was, at one time, in charge of the Genetics nurses. She was an exceptionally fine woman. If memory serves me correctly, Mildred and Marion both came to ABCC from Duke University, and I think it was Grant Taylor who recruited them. You may remember that he too had come from Duke where he was Associate or Assistant Dean of the Duke Medical School.

Warmest regards,

Jack Schull
(former RERF Vice Chairman)

The recent issue of *RERF Update* was interesting with RERF's involvement in the Tohoku disaster and Dr. Schull's historical article.

Dr. Schull has experienced the transition of ABCC and Hiroshima city from 1947 when he first arrived to the present RERF and the modernization of the city because of his involvement all these years. The readers undoubtedly are appreciative of learning what had transpired in those years when Japan was slowly recovering from the vast destruction.

Sincerely,

Merry Y. Uemoto
(former secretary to Dr. William J. Schull)

Responses to the Fukushima Dai-ichi Nuclear Power Plant Crisis

Immediately after the nuclear power plant crisis occurred on March 11, 2011, RERF convened its Committee for Radiation Emergency Medical Response (Chair: Chief Scientist Kazunori Kodama, Vice Chair: Information Technology Department Chief Hiroaki Katayama) and has since adopted the following measures based on deliberations led by the relevant committee:

1. Dispatch of experts to affected regions and radiation measurement

a. Dispatch of a radiation technologist to Fukushima prefecture for radiation measurement, March 16–22, 2011

Mr. Toshinori Kurisu, Assistant Chief of Technicians in the Department of Clinical Studies, was dispatched to Fukushima prefecture as a member of an emergency assistance team sponsored by the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE). This team (six members) was organized to respond to Fukushima prefectural government's request to the Hiroshima prefectural government. In Fukushima, together with the staff of local health and welfare offices and public health centers, the team members visited 12 evacuation sites, where they conducted radiation measurements using radiation survey meters and provided consultation services to the evacuees.

b. Dispatch of a research scientist and a radiation technologist to Yamagata prefecture for providing guidance and training regarding radiation measurement, March 17–24, 2011

Dr. Norio Takahashi, Research Scientist in the Department of Genetics, and Mr. Katsuhisa Yamasaki, Senior Technician in the Department of Clinical Studies in Nagasaki, were dispatched by RERF at the request of the Yamagata prefectural government via Japan's Ministry of Health, Labour and Welfare. Dr. Takahashi and Mr. Yamasaki visited four public health centers and six evacuation sites in Yamagata prefecture, providing guidance and training regarding radiation measurement using radiation survey meters.

c. Radiation measurement at RERF Hiroshima

At the request of 33 persons (as of August 26) who had moved to Hiroshima from areas near the nuclear power plant, Dr. Asao Noda, Assistant Chief, Department of Genetics, and other relevant staff conducted radiation measurements of the individuals using radiation survey meters.

2. Information provision and consultation regarding radiation and health

a. Responses to inquiries from the general public and media

Since March 11, the date of the start of the cri-

sis, RERF has been inundated with general public inquiries and media requests for information. During the first three days (including Saturday and Sunday) after the initial disaster, Chairman Toshiteru Okubo received more than 50 telephone inquiries regarding a wide variety of issues, not just about research themes pursued by RERF. Based on such inquiries, on March 14, the chairman prepared a list of the most frequently asked questions, to which Dr. Nori Nakamura, Chief Scientist, provided model answers. Since that day, the resulting Q&A manuals have been shared among all employees, while Dr. Nakamura has mainly responded to inquiries from the media and the Public Relations and Publications Office to inquiries from the general public. The Departments of Clinical Studies and Epidemiology have responded to inquiries from the Adult Health Study and the Life Span Study subjects, respectively.

b. Creation of a special webpage

On March 15, on its website's "What's New" page, RERF notified the general public of availability of brochures regarding radiation health effects. On March 17, a special webpage related to the nuclear power crisis was created, and thereafter RERF website access dramatically increased (see Facts and Figures).

3. Biological dose assessment

Dr. Yoshiaki Kodama, Chief of the Department of Genetics and member of the Chromosome Network Committee sponsored by the National Institute of Radiological Sciences, has been placed on standby in case of occurrence of high-level radiation exposure, maintaining the emergency liaison system within the network. Since chromosome-based dose assessment is time-consuming and labor-intensive, and RERF is capable of conducting such assessments for only an estimated 40–50 cases, it was decided that RERF would accept requests only from the said network and the Hiroshima University Radiation Emergency Medicine Promotion Center, a tertiary referral medical institute for western Japan (to date no requests for biological dose assessments have been received at RERF).

4. Preparation for long-term epidemiological research

To prepare for the possibility of long-term epidemiological research on residents of the affected areas, discussions on how to carry out such research were initiated on March 15. Thereafter, with increased worldwide attention on the nuclear power plant crisis, international organizations, governmental agencies, and research institutes might be expected to turn to RERF's history and experience in conducting long-term epidemiological research.

With that in mind, RERF Chairman Okubo proposed to member institutions of the Council of Radiation Effects Research Organizations on March 29 establishment of a system for conducting long-term epidemiological research. The Council held an ad hoc meeting at the Fukushima Medical University on April 2. On April 25, a group of observers from the Fukushima Medical University visited RERF. On April 27, the sixth working meeting of the Council of Radiation Effects Research Organizations was held in Tokyo, attended by Dr. Okubo and Dr. K. Kodama. The Council decided to nominate advisors for radiation dose estimation and long-term epidemiological research from among the Council members.

5. Cooperation in a health management study to be conducted by the Fukushima Medical University

On May 13, a preparatory meeting for a committee to review Fukushima health studies was held at the Fukushima Medical University, attended by Dr. K. Kodama and Dr. Kotaro Ozasa, Chief of the Department of Epidemiology. On May 20, the Fukushima prefectural government called on RERF to recommend a candidate to serve as a member of a review committee for the prefecture's Health Management Study on Fukushima Residents (hereinafter referred to as "Fukushima Health Management Study"). In response, it was decided that Dr. K. Kodama would assume the position of committee member. On May 25 and 26, Professor Seiji Yasumura from the Fukushima Medical University, as well as employees in charge at the Fukushima prefectural government, visited RERF and toured the Departments of Epidemiology and Clinical Studies. Subsequently, the visitors exchanged opinions and held deliberations with RERF staff members.

On May 27, the first meeting of the Fukushima Health Management Study Review Committee was held at the Fukushima Prefectural Jichi-Kaikan, where the Fukushima prefectural government and the Fukushima Medical University officially announced that a health study of Fukushima residents would be conducted. On June 8, the first meeting in fiscal year 2011 of the Radiation Dose Estimation Expert Panel was held at the Fukushima Medical University, attended by Dr. Ozasa. On June 12, the first meeting of the headquarters for implementation of the Fukushima Health Management Study (FHMS) was held at the Fukushima Medical University, attended by Dr. K. Kodama and Dr. Ozasa. On June 18, the second meeting of the FHMS Review Committee was held at the Fukushima Prefectural Jichi-Kaikan, attended by Dr. K. Kodama. At the relevant meeting it was

decided that a basic survey (questionnaire) would be conducted to estimate radiation dose to which Fukushima residents were exposed and that the relevant survey would be commenced around the end of June, starting with areas of relatively high contamination.

On July 24, the third meeting of the FHMS Review Committee was held at the Fukushima prefectural government offices, attended by Dr. K. Kodama and Dr. Ozasa. At this meeting, discussions were held regarding implementation of the basic study as well as more specific studies, including health examinations for those residing in the evacuation and other restricted areas and a thyroid study for children. On August 12, RERF and the Fukushima Medical University entered into a collaboration agreement in the fields of education, research, and health (see RERF News). The fourth meeting of the FHMS Review Committee was held on October 17 in Fukushima and Dr. K. Kodama attended. A summary of an international symposium (see below) was reported and the progress of the thyroid study was also discussed at the meeting. With regard to the health management study targeting about two million Fukushima residents, RERF will continue to provide know-how to the project, utilizing the foundation's experience accumulated through its follow-up of A-bomb survivors in Hiroshima and Nagasaki.

Drs. Okubo and K. Kodama participated in the *International Expert Symposium in Fukushima—Radiation and Health Risks* held in Fukushima on September 11 and 12, 2011. Dr. Kiyohiko Mabuchi, former chief of RERF's Epidemiology Department and currently Deputy Chief of the U.S. National Cancer Institute's Radiation Epidemiology Branch also participated. The purpose of the symposium was for a group of international and Japanese experts in radiation and health-related fields to review the potential health effects of radiation from the Fukushima nuclear accident.

The symposium was also attended by experts from relevant international, intergovernmental bodies including the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the World Health Organization (WHO) and the International Atomic Energy Agency (IAEA) and by representatives of non-governmental organizations including the International Commission on Radiological Protection (ICRP). The symposium participants took note of the wide global experience available for assessing the consequences of major releases of radioactive substances into the environment, which have resulted from the international review of the aftermath of large accidents, such as the Chernobyl accident. The conclusions and recommendations that emerged from the symposium included the following two that are especially relevant to RERF: (1) "Because of the long-term support to persons exposed to radiation in Hiroshima and Nagasaki by Japanese health professionals and scientists during the past 60 years, Japan has considerable expertise, probably the best in the world, in radiation-related issues. That expertise should be called upon to help those affected by the Fukushima nuclear accident. At the same time it is important to recognize the responsibility of the authorities to learn as much as possible from the information obtained." and (2) "Health professionals and scientists must seek to explain the possible effects or lack of detectable effects of radiation to the best of their ability to the people of Fukushima and other concerned individuals. Transparency in dose evaluation, risk assessment and decision-making is vital. At the same time, the scientific evidence and understanding must be provided to the public in a manner that can be readily understood."

RERF's Dr. Waka Ohishi (Assistant Chief of the Department of Clinical Studies) has been consulted by Fukushima Medical University regarding methodologies for storage of biological specimens at RERF. They need the information to help them develop storage systems for the FHMS.

6. Advice to the government and other organizations

On April 1, Dr. K. Kodama, Chief Scientist, was appointed as one of the policy investigators (seven experts with medical licenses) serving the Cabinet Secretariat to provide advice regarding medical responses to the Fukushima nuclear power plant crisis. Thereafter, Dr. K. Kodama has engaged in the relevant work two days each week.

In November, Dr. K. Kodama was also appointed as an advisor to serve on the Advisory Committee on Radiation and Health for Fukushima Prefecture. During the same month, Dr. Roy E. Shore, Vice Chairman, was appointed to serve as an advisor to the Health Risk Assessment Working Group on the Fukushima Dai-ichi Nuclear Power Plant Accident, a working group of the WHO.

Mr. Toshinori Kurisu (right) measuring the soil contamination in Fukushima prefecture as a sub-leader of the HICARE's radiation-dose measurement team

The First Meeting of the Board of Councilors Held in Hiroshima

The first meeting of the Board of Councilors was held at RERF's Hiroshima Laboratory over the two days of June 21 and 22. The Board of Councilors, newly established with RERF's status change this April to an exceptional incorporated foundation with councilors, is a decision-making body replacing the former Board of Directors. Of the total of eight Councilors, seven were in attendance at the meeting, with representatives from the U.S. and Japanese governments also present. The Councilors discussed RERF's activities report, settlement of accounts report, activities plan, and working budget, as well as other agenda items such as procedures for transition to a public-interest incorporated foundation (PIIF), RERF's response to the Fukushima Dai-ichi nuclear power plant crisis, and appointment of Directors.

In the meeting's opening remarks, the representatives from the U.S. and Japanese governments indicated that they would provide RERF with continued support. The main topics discussed at the meeting were the FY2010 activities report, settlement of accounts, and audit reports, with the settlement of accounts approved as drafted. The activities report touched on RERF's responses to the ongoing Fukushima Dai-ichi nuclear power plant crisis, followed by Councilors' comments calling for RERF's more active involvement in the situation.

The Councilors approved, as drafted, FY2011 plans for research activities including the clinical study of A-bomb survivors' children, research on individual radiation doses, and collaborative projects with other organizations, as well as the FY2011 working budget. Regarding the 12th plan for decreases in budgeted personnel slots, initiated in FY2010, it was reported that the number of employees would be reduced by five in the current fiscal year.

A report concerning the 38th Scientific Council meeting, at which detailed review of the Departments of Epidemiology and Statistics was conducted, outlined general recommendations calling for improvement of research quality and development of research plans based on priorities that take into consideration contemporary relevance and other factors, as well as five specific recommendations. Discussion about RERF's responses to those recommendations then followed.

The ongoing procedures for transition to PIIF status were explained, as follows: RERF obtained the competent minister's approval for change of its Act of Endowment and transitioned to an exceptional incorporated foundation with councilors in April of this year for an improved operational structure toward becoming a PIIF; in addition to the legally stipulated organizations, RERF also explained its establishment of a Scientific Advisory Committee and appointment of Local Advisors. The Councilors approved a draft application for status-change approval and a draft Articles of Incorporation. It was then reported that RERF was scheduled to submit the application to Japan's Cabinet Office and to complete transition to PIIF status by April 2012.

Lastly, the Councilors appointed three Directors, two Scientific Advisors, and two Local Advisors.

Participants of the first meeting of the Board of Councilors (Hiroshima Laboratory)

Hiroshima and Nagasaki Local Liaison Council Meetings

The Hiroshima and Nagasaki Local Liaison Councils, established to incorporate into RERF's operations local community input regarding maintenance of the health and improvement of the welfare of atomic-bomb survivors, consist of representatives of related local organizations, including universities, medical institutions, A-bomb survivors' organizations, prefectures, municipalities, and other leaders in their field.

The 20th meeting of the Nagasaki Local Liaison Council was held at the Nagasaki Laboratory on July 14, 2011. Following greetings by Chairman Toshiteru Okubo and Dr. Shigeru Katamine, President of Nagasaki University and chairman of the Nagasaki Local Liaison Council, RERF reported on its present status, recent research activities and results, and its clinical study of second-generation atomic-bomb survivors (F_1 clinical study). The status of RERF's collaborative study with the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and RERF's public relations activities, including public lectures in Hiroshima and Nagasaki, were also touched on. In response to the abovementioned presentations, the council members asked several questions, such as methods used for assessment of internal radiation exposure, proper recognition of psychological and mental effects of radiation exposure, and locating F_1 clinical study participants who happen to change addresses.

RERF also made a report concerning its response to the Fukushima Dai-ichi nuclear power plant crisis to the effect that RERF, in collaboration with other institutions concerned, intends to strengthen its support for and cooperation in long-term epidemiological studies in Fukushima. Council members provided RERF with many valuable opinions about RERF's plan. The 20th meeting concluded with Dr. Katamine's closing remark that the council encourages RERF to fully review the opinions expressed at the meeting and incorporate them into its operations.

The Hiroshima Local Liaison Council held its 17th meeting on July 27 at the Hiroshima Laboratory. At the meeting chaired by the council chairman Dr. Toshimasa Asahara (President of Hiroshima University), RERF made the same reports that it did in Nagasaki and, as was the case for the meeting in Nagasaki, the council members expressed various opinions. In particular, a strong request was made for relocation of the Hiroshima facilities, as also happened at the last year's meeting. RERF's report on its response to the Fukushima Dai-ichi nuclear power plant crisis led to active discussion concerning RERF's support for long-term epidemiological studies in Fukushima and strengthening of collaborative arrangements with other institutes. RERF reported that it had agreed with Fukushima Medical University to sign a collaborative agreement on education, research, and health care in order to allow RERF to use its expertise and experience accumulated through long-term studies of atomic-bomb survivors in health surveys to be conducted among residents in the affected area.

The 17th Hiroshima Local Liaison Council meeting

First Public Lectures for Citizens Held in Nagasaki

As a result of the success of the first public lectures in Hiroshima, RERF sponsored its first public lectures for citizens in Nagasaki at a hall of the Nagasaki Atomic Bomb Museum from 1:30 to 4:00 in the afternoon of July 16 (see cover photo). The open lecture program for citizens was planned to promote exchange between citizens and RERF staff by providing readily understandable explanations to the general public including A-bomb survivors on research achievements concerning health effects of A-bomb radiation obtained at RERF over many years. More than 180 people attended.

The public lecture program consisted of two lectures. First, Chief Scientist Kazunori Kodama spoke on "Radiation and cancer risk," explaining how much increase in risk of cancer, including leukemia, has been observed due to radiation exposure, based on results of long-term health effects

studies. Next, Chief Scientist Nori Nakamura gave a lecture titled "Studies on children of A-bomb survivors conducted thus far," introducing research results involving such topics as birth abnormalities, chromosome aberrations, mortality, cancer incidence, and the absence of detected effects in children who were born to parents who had been exposed to A-bomb radiation.

At the beginning of the program, following greetings by Chairman Toshiteru Okubo, Dr. Yuji Nagayama, Director of the Nagasaki University Atomic Bomb Disease Institute, read a message from Dr. Shun-ichi Yamashita (former Dean of the Nagasaki University Graduate School of Biomedical Sciences), who had assumed the position of Vice President of Fukushima Medical University on the previous day. Before a question-and-answer session, Dr. Masao Tomonaga, Director of the Japanese Red Cross Nagasaki Atomic Bomb Hospital, made special remarks about the relationship between Nagasaki and RERF. In this question-and-answer session, many questions were raised, including those about internal and external exposure caused by nuclear power plant accidents. Even after the program ended, some citizens remained in the hall eagerly asking questions.

Open House Events in Hiroshima and Nagasaki

August 5 and 6 and August 8 and 9, RERF held its annual Open House in Hiroshima (17th annual event) and Nagasaki (15th annual event), respectively, under the theme "Radiation and health sciences." With enhanced public interest in radiation due to the Tokyo Electric Power Company's Fukushima Dai-ichi nuclear power plant crisis, the events this year featured a special exhibition introducing the basics of radiation and its effects on human health, in addition to the regular exhibitions of our latest research results.

At the Hiroshima Laboratory, a specialist's corner set up next to the abovementioned special exhibition corner, attracted many visitors eager to ask questions, including families with children. In the event's public lectures, which have become part of the regular program in Hiroshima, Dr. Asao Noda, Assistant Chief of the Department of Genetics, and Chief Scientist Nori Nakamura spoke about "What is radiation?" on the 5th and 6th, respectively, and on the 6th, Dr. Kotaro Ozasa, Chief of the Department of Epidemiology, spoke on the theme "What is radiation epidemiology?" Compared with the two lectures of last year's event, this year's Open House had three lectures attended by large enthusiastic audiences who asked many questions even after the lectures were concluded. The Hiroshima Laboratory's Open House drew 1,375 visitors for the two days.

The Nagasaki Laboratory also prepared special exhibition posters introducing the basics of radiation science. Information about the efforts of RERF employees who were dispatched to Fukushima prefecture to assist in that prefecture's response to radiation exposure, such as radiation measurement and screening, and to Yamagata prefecture to help people evacuated from Fukushima to Yamagata, was also introduced. The special exhibition attracted many visitors, including families with children, who listened intently to explanations provided by researchers in front of the posters illustrating basic information about radiation and its human health effects. Despite occasional heavy rain on both days of the event, all of the hands-on exhibitions attracted many visitors as usual. Nagasaki Laboratory's Open House drew 390 visitors for the two days.

Q & A corner in the Hiroshima Open House

Open House at the Nagasaki Laboratory

RERF and Fukushima Medical University Sign a Collaborative Agreement

RERF and Fukushima Medical University, in the wake of the nuclear crisis at the Tokyo Electric Power Company's Fukushima Dai-ichi nuclear power plant, agreed to strengthen their collaborative relationship in the fields of education, research, and public health, signing a collaborative agreement at the university on August 12, 2011.

The agreement aims at further development of both organizations and establishment of a pioneering educational/research center concerning health effects of radiation through promotion of educational and academic research activities in the field of radiation effects research, closer interactions between university faculty members and RERF researchers, and improvement of the health and welfare of residents of Hiroshima, Nagasaki, and Fukushima prefectures.

In addition, aside from health effects of direct A-bomb radiation exposure, which RERF has investigated on its own over many years, progress is expected in research on health effects of internal exposure to low-dose radiation and lifetime cumulative exposure, the types of radiation exposures from the radioactive contamination emitted in the Fukushima catastrophe and currently causing public concern.

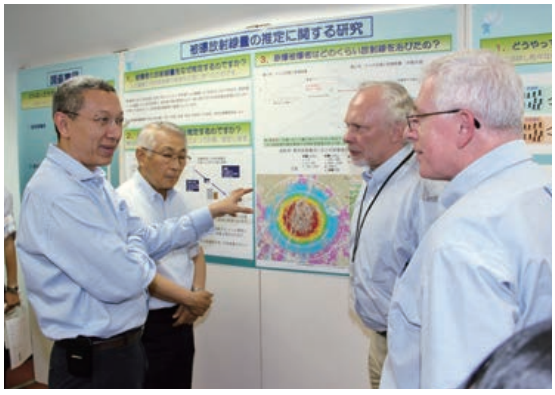
On the same day, Fukushima Medical University also signed a collaborative agreement with the National Institute of Radiological Sciences.

(from left) Dr. Yoshiharu Yonekura, President, National Institute of Radiological Sciences, Dr. Shin-ichi Kikuchi, President, Fukushima Medical University, and RERF Chairman Toshiteru Okubo

IAEA's Deputy Director General and Other Officers Visit RERF

RERF received visits from four officers of the International Atomic Energy Agency (IAEA) during the period from August through November, 2011. On August 5 and September 15, Dr. Rethy Chhem, Director of Division of Human Health, Department of Nuclear Sciences and Applications, and Dr. Jan Wondergem, Applied Radiation Biology and Radiotherapy Section, visited RERF's Hiroshima Laboratory, respectively. On November 22, Dr. Daud Mohamad, Deputy Director General and Head of Department of Nuclear Sciences and Applications, visited RERF, with Dr. Eduardo Rosenblatt, Head of the Applied Radiation Biology and Radiotherapy Section, Department of Nuclear Sciences and Applications.

Dr. Rethy Chhem, who visited during our Open House event, was in Hiroshima to exchange opinions on research collaboration with the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE). He was guided by RERF Chairman Toshiteru Okubo on a tour of RERF's posters on the foundation's history, chromosomal changes caused by radiation, dosimetry systems used for the A-bomb survivors, collaborations between IAEA and RERF, and a summary of the activities of HICARE. Later in the Chairman's Office, Vice Chairman Roy E. Shore explained RERF's recent research results to Dr. Chhem, leading to an active exchange of questions and answers.



(from left) Dr. Rethy Chhem of IAEA, RERF Chairman Toshiteru Okubo, Statistics Department Chief Harry Cullings, and Vice Chairman Roy Shore

Dr. Wondergem is an expert in the field of biodosimetry based on chromosomal aberrations and plays a core role in research collaboration between the IAEA and HICARE. After being greeted by the chairman and senior staff, he toured the facilities, including the biological specimen storage facilities, led by Chief Scientist Kazunori Kodama. Dr. Wondergem subsequently had a substantive discussion regarding collaborative research programs with the chiefs and assistant chiefs of the Departments of Genetics and Radiobiology/Molecular Epidemiology.

IAEA Deputy Director General Mohamad and Dr. Rosenblatt, who visited RERF in November, were briefed on RERF's current status, future plans, and research activities by Chairman Okubo and Vice Chairman Shore. They were guided by the chairman and other senior staff on a tour of the facilities, including the Departments of Genetics and Epidemiology. Drs. Mohamad and Rosenblatt visited RERF on the occasion of being in Hiroshima to attend the 2011 HICARE International Symposium "The Effects of Radiation on the Human Body—Toward Establishing an International Network for Medical Care for the Radiation-exposed," held on November 23 in cooperation with IAEA, where they gave keynote speeches and Dr. Mohamad served as a commentator in the symposium.

IAEA Deputy Director General Daud Mohamad (second from right) and Dr. Eduardo Rosenblatt (background left) with RERF Chairman Toshiteru Okubo (right) as they depart RERF

Ambassador Mari Amano, Delegation of Japan to the Conference on Disarmament, Visits RERF

Ambassador Mari Amano, from the Delegation of Japan to the Conference on Disarmament, visited the Hiroshima Laboratory on September 16. The Delegation is an organ that deals with the Conference on Disarmament held in Geneva, the First Committee of the United Nations General Assembly held in New York, and other international disarmament meetings held around the world, thereby advancing Japan's disarmament diplomacy.

Mr. Amano toured the RERF facilities after being briefed on the organization's current status and research activities by Chairman Toshiteru Okubo and other officers. Mr. Amano, who was appointed to the position of Japan's ambassador to the Conference on Disarmament on September 1, 2011, came to Hiroshima for the purpose of making a courtesy visit to the mayor of Hiroshima. He visited RERF to gain a general understanding of RERF's research studies.

Ambassador Mari Amano, from the Delegation of Japan to the Conference on Disarmament (far left) being briefed by the directors and senior staff of RERF

Staff News

Midori Soda, Assistant Chief in the Department of Epidemiology, Nagasaki, and **Mieko Kodaira**, Laboratory Chief of Biochemical Genetics, Department of Genetics, reached mandatory retirement age on December 31, 2010 and June 30, 2011, respectively. Dr. Soda was re-employed as a Research Scientist in the same department as of January 1, 2011 and Dr. Kodaira was re-appointed as Laboratory Chief as of July 1.

In the Laboratory of Cytogenetics, Department of Genetics, Laboratory Chief **Asao Noda** was promoted to Assistant Department Chief, and **Yuko Hirai**, Senior Scientist, was promoted to Laboratory Chief to replace the former laboratory chief Noda on July 1. In the Department of Clinical Studies, **Waka Ohishi**, Division Chief of Clinical Laboratories, was promoted to Assistant Department Chief effective from August 1.

Ravindra Khattree resigned effective August 15 as a Senior Scientist in the Department of Statistics. He returned to the U.S. where he is a Professor in the Department of Mathematics and Statistics at Oakland University in Rochester, Michigan. As of November 1, **Norio Takahashi**, Research Scientist, transferred to the Department of Radiobiology/Molecular Epidemiology from the Laboratory of Biochemical Genetics in the Department of Genetics.

Visiting Student Researchers

Sandra Jaudzema, MD

I am a trainee (from June 1 to July 28, 2011) in the field of pathology from Latvia. Latvia is a small but very beautiful country on the sandy coasts of the Baltic Sea with its wonderful capital Riga. My country is rich in beautiful nature and various culture traditions—especially singing.

I graduated from the University of Latvia Faculty of Medicine in 2010. Currently I am studying at the Department of Continuing Education in Riga Stradins University and working at Pauls Stradins Clinical University Hospital's Institute of Pathology. Work at the hospital is one of my trainee duties. Additionally I also work as a lecturer at the Department of Pathology in Riga Stradins University Faculty of Medicine.

It was a great opportunity for me to study and work in the Radiation Effects Research Foundation (RERF) and the experience was very important for my education and my development of professional skills. In RERF's Immunology Laboratory, I was trained in the effects of radiation exposure on immune function, especially using methods to measure intracellular reactive oxygen species levels in plasma samples, to prepare lymphocyte cell subsets, and to examine genomic instability. I am very grateful for this chance and would like to express my gratitude to the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) and RERF for the opportunity to participate in the RERF Training Program. I would also like to express my deepest gratitude to the staff of the Department of Radiobiology/Molecular Epidemiology for their great support and warm-heartedness, especially to Dr. Tomonori Hayashi who guided and supervised me through this delicate world of science.

Sandra Jaudzema, MD (right) with Dr. Tomonori Hayashi at the Immunology Laboratory

Luzhou Xu, MD, PhD

I am a physician at the affiliated hospital of Nanjing University of Traditional Chinese Medicine (TCM) in Nanjing, China, and I also received my PhD there. Our hospital is one of the national clinical research centers. Although I did some clinical and basic research work in the last five years, I am aware of my insufficiencies and I need more laboratory training to further my scientific career.

I arrived at Hiroshima University in early June 2011, and then came to the Genetics Department of RERF. I am honored to have been accepted as a visiting research fellow here.

At the guidance of Dr. Asao Noda, I joined his team and focused on the mechanisms of DNA dou-


Luzhou Xu, MD, PhD

ble-strand break repair following ionizing radiation. I like this challenge because it is entirely different from my former work in China. I used to read Chinese publications but now I'm reading the international top journals such as *Nature*, *Science*, and *Cell*, and performing some gene-manipulation experiments. I changed my idea for research from pathophysiology to cell signaling. I'm interested in whether Chinese herbs have something to do with the repair mechanisms of double-strand breaks or recovery from radiation injury. I am expecting to get good results.

In RERF, I enjoy working with such diligent scientists. We are able to exchange our ideas, discuss our outcomes, and remark about our conclusions. I thank RERF's amicable and unselfish scientists and staff who have been so helpful. I think my days in RERF will be an important memory in my life.

Ayako Takamori


Ayako Takamori

I am a doctoral student in the biostatistics program at Kurume University's Graduate School of Medicine, and I am here at RERF as a visiting student fellow in the Department of Epidemiology. Immediately after I was born in Hiroshima, my parents moved my family to Tokyo, then to Ehime prefecture, and finally back to Hiroshima. When in Ehime, I attended Matsuyama Higashi High School, where Natsume Soseki, a famous Japanese writer, once taught (located near Dogo Onsen Spa).

I have had a strong interest in researching social medicine ever since I was young. While I was taking general education classes during my master's program at Kyushu University's Graduate School of Medical Sciences, in which I enrolled to study medical care systems assessment, I encountered the field of statistics. Just as I was worried about ever finding an opportunity to study statistics further, I came to know of the Kurume University Biostatistics Center. When I learned that Kurume University had a partnership agreement with RERF, I decided to enter the Center's program hoping to become involved in research of the health effects of the A-bomb survivors, an area of study in which I have always wanted to take part. Since then I have been working diligently to enhance my knowledge of medical statistics based on mathematical statistics. With this internship opportunity, I was able to add even more motivation to research and develop a research protocol titled "Mortality analysis of the Life Span Study (LSS) cohort taking into account multiple causes of death indicated in death certificates" in June 2011. The objective of the project is to study association between radiation and underlying/secondary (other than underlying) causes of death that were identified from those indicated in the death certificates of A-bomb survivors who had been registered as LSS subjects.

At RERF, research scientists and administrative staff have been so kind to me for which I am very grateful. Although I am shy and easily become nervous around strangers, the friendliness of people at RERF makes me relaxed, and as days go by, it is easier for me to talk to people, which has become one of my pleasures at RERF. I am grateful for the instructions I receive at RERF in terms of English and practical study methods. During the course of this fiscal year, I will travel back and forth between Kurume and Hiroshima to make progress on my study. I am firmly determined to work hard to complete my analysis and write a paper as soon as possible. Thank you very much.

Recognition Received by an RERF Scientist

Dr. Waka Ohishi, Assistant Chief, Department of Clinical Studies, was recognized recently by the Editor-in-Chief of the journal of the American Association for Cancer Research, *Cancer Epidemiology, Biomarkers and Prevention* (*CEBP*). In his letter to Dr. Ohishi, *CEBP* Editor-in-Chief Timothy A. Rebbeck said:

"Congratulations! Your article 'Risk factors for hepatocellular carcinoma in a Japanese population: A nested case-control study' is one of the most cited 2008 *CEBP* articles from Japan. We appreciate your excellent contribution to our journal and hope you will consider *Cancer Epidemiology, Biomarkers and Prevention* for your future manuscripts."


Waka Ohishi, MD, PhD

Recently, Dr. Ohishi was promoted to Assistant Chief in the Department of Clinical Studies (see Staff News). A 2011 follow-up paper to her 2008 paper is summarized by Dr. Ohishi in this current issue of *RERF Update* (see Science Articles).

The 52nd meeting of the Late A-bomb Effects Research Association

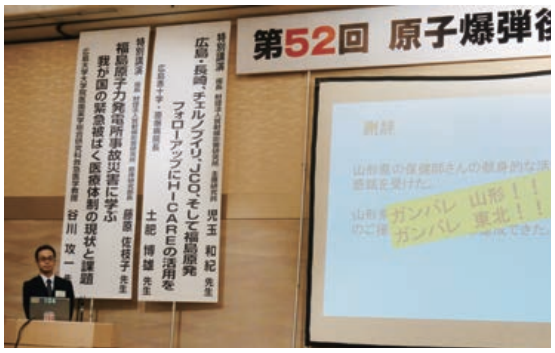
Kanya Hamasaki, Research Scientist
Laboratory of Cytogenetics, Department of Genetics

The 52nd meeting of the Late A-bomb Effects Research Association was held on June 5, 2011 at the hotel Hacchobori Chanter. The opening address by Dr. Saeko Fujiwara, Chief of the RERF Department of Clinical Studies, Hiroshima, and this year's meeting organizer, marked the beginning of the meeting program consisting of two special lectures, one symposium, and 29 general presentations.

In the first of the special lectures, titled "Utilization of HICARE's (Hiroshima International Council for Health Care of the Radiation-exposed) expertise in the follow-ups of Hiroshima, Nagasaki, Chernobyl, the nuclear fuel processing company JCO accident, and the Fukushima nuclear power plant crisis," Dr. Hiroo Dohy, Director of the Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, talked about the atomic bombings, several radiation accidents, and HICARE's history. He said that a long-term health survey needs to be conducted for the victims of radiation contamination in the Fukushima nuclear power plant crisis and that it is desirable for follow-ups to be based on HICARE's framework. In the second special lecture, Dr. Koichi Tanigawa, Professor at the Emergency and Critical Care Medicine, Graduate School of Biomedical Sciences, Hiroshima University, gave a lecture titled "Lessons from the Fukushima nuclear power plant disaster: Present status and challenges of Japan's emergency medical care system." Dr. Tanigawa, who reestablished the radiation emergency medical response system that had become dysfunctional in the affected areas after the crisis, laid out some of the problems identified in the crisis, such as dysfunctional chain of command in the national government, insufficient information on radiation, incomplete systems for medical care of the radiation-exposed, and underestimation of the importance of radiology in medical school education.

Those lectures were followed by a symposium on the theme "Global dissemination of results from research on late effects of radiation." Dr. Kenji Kamiya, Director of the Hiroshima University Research Institute for Radiation Biology and Medicine (RIRBM), Dr. Shun-ichi Yamashita, Dean of the Nagasaki University Graduate School of Biomedical Sciences, and Mr. Takanobu Teramoto, RERF Executive Director, talked about global dissemination of results from research on late effects of radiation and scientific information at their respective institutes. Dr. Satoru Ubuki, a former RIRBM researcher, spoke about Hiroshima's history of information communication relating to the damage caused by the atomic bombing. In addition to those four symposiasts, two speakers gave designated remarks: Mr. Masaya Yamauchi, assistant chief editorial writer at the Chugoku Shimbun, spoke on the topic of radiation risks from the Fukushima and Chernobyl nuclear accidents from the viewpoint of a news reporter; and Mr. Koichiro Maeda, Director of the Hiroshima Peace Memorial Museum, talked about the present status of the museum's displays and renewal plans.

The 29 general presentations were all delivered orally, and included 13 related to clinical or epidemiological studies of the atomic bombings of Hiroshima and Nagasaki, 12 related to basic research into radiation exposure based on animal or cell experiments, and four related to radiation contamination from the Fukushima nuclear power plant crisis. Representing RERF, Mr. Katsuhisa Yamasaki, Senior Technician of the Department of Clinical Studies, Nagasaki, who visited Yamagata prefecture with Dr. Norio Takahashi (Research Scientist, Department of Genetics), made a presentation titled "Support for people evacuated to Yamagata prefecture due to the nuclear power plant crisis." Dr. Yoshiki Tanakamaru, Chief of the Nuclear Scanning Section, Central Radiology Division, Department of Radiology, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, who led the team dispatched by HICARE to Fukushima, which Mr. Toshinori Kurisu (Assistant Chief of Technicians, Department of Clinical Studies, Hiroshima) also joined, made a presentation titled "HICARE assistance in the Fukushima



RERF's Mr. Katsuhisa Yamasaki speaking about his activities in Yamagata prefecture in March 2011

nuclear power plant crisis."

The top concern at this meeting was the Fukushima nuclear power plant crisis, which had spiraled out of control immediately after the Great East Japan Earthquake on March 11 and still has not come to an end. The crisis was discussed in both of the two special lectures and referred to in the symposium and some of the general presentations, reminding the audience of the magnitude of the radioactive contamination from the Fukushima crisis. I also felt the motivation of the participants of this meeting to use the experience and expertise accumulated in Hiroshima and Nagasaki to help Fukushima in various areas, including mitigation of damage caused by harmful rumors and follow-up health surveys of its residents. RERF surely will play a major role and bear great responsibility in such support efforts. This meeting encouraged my desire to be of help to such efforts in some fashion.

The Second Epidemiological Training Workshop for Biologists

Nori Nakamura, Chief Scientist

On September 26–27, 2011, the Epidemiological Training Workshop for Biologists, hosted by the Council of Radiation Effects Research Organizations, was held at the RERF Auditorium in Hiroshima. This year's event turned out to be a lively gathering, attracting over 80 scientists (56 non-RERF and 26 RERF participants). (The Council of Radiation Effects Research Organizations, consisting of Fukushima Medical University, Hiroshima University, the Institute for Environmental Sciences, Nagasaki University, the National Institute of Radiological Sciences, the Radiation Biology Center [Kyoto University], and RERF [in alphabetical order], was established to facilitate mutual understanding and collaboration among radiation effects research organizations.)

On the first day of the workshop, RERF Chairman Toshiteru Okubo gave opening remarks, and the participants introduced themselves. Dr. Ritsu Sakata, Department of Epidemiology, then delivered lectures titled "Overview of epidemiological studies (including explanation of terms)" and "Calculation of low-dose risks (practical training)." Following those lectures, Dr. Kotaro Ozasa, Chief of the Department of Epidemiology, and Mr. Eric Grant, from the same department, spoke on the theme "Low-dose risks are difficult," with Dr. Nori Nakamura, Chief Scientist, and Dr. Yukiko Shimizu, Department of Epidemiology, then discussing "Breast cancer risk and childhood susceptibility (age dependence)." In the afternoon, Professor Michiaki Kai, Oita University of Nursing and Health Sciences, and Professor Emeritus Ohtsura Niwa, Kyoto University, gave talks titled "Childhood susceptibility of thyroid cancer" and "Age susceptibility from the viewpoint of biological mechanisms," respectively, with a general discussion held under the theme "What is radiation biology's aim?" The second day's lectures were titled "Fetal radiation susceptibility" (delivered by Chief Scientist Nori Nakamura and Dr. Hiromi Sugiyama, Department of Epidemiology), "Childhood susceptibility to leukemia" (by Dr. Nori Nakamura) and "Genetic radiation effects" (by Dr. Nori Nakamura).

Due to the situation at the Fukushima Dai-ichi nuclear power plant caused by the earthquake that struck the Tohoku region in March, participants engaged in active questions and answers with a strong interest in that particular issue. A specific question regarding how to respond to questions of the kind that were actually asked in Fukushima was raised. Some lectures included many abbreviations that not everyone could understand, forgetful of the fact that the workshop was intended for communication across different fields of research. However, many participants are seeking just this kind of workshop for learning and interaction, and thus for us to continue to offer such opportunities is deemed important.

The discussion went around in circles at one

Participants of the second epidemiological training workshop for biologists

point due to lack of accurate understanding of relative risk, absolute risk and lifetime risk, but the participants ultimately seemed to gain a good understanding overall. In response to a request by the epidemiologists, we would very much like to plan a biological training workshop for epidemiologists, which RERF staff members alone should be able to organize easily. Our future challenge seems to be the creation of common research themes, shared between RERF scientists and outside researchers, on the occasion of such gatherings.

The 14th International Congress of Radiation Research—A Meeting of Science and History

Evan B. Douple, Associate Chief of Research

The largest meeting of radiation scientists in the world is typically the International Congress of Radiation Research (ICRR) which is held approximately every four years. The 14th ICRR was held for the first time in Warsaw, Poland, from August 28 to September 1, 2011. It was very fitting that the meeting was hosted by the Maria Skłodowska-Curie Polish Radiation Research Society, since the meeting celebrated the 100th anniversary of the Nobel Prize awarded to Maria Skłodowska-Curie for the separation and characterization of radium and polonium. That was the second time for the famous scientist who was born in Warsaw to receive the award—in 1903 she was awarded the Nobel Prize for Physics along with her husband Pierre and Henri Becquerel. Some readers may have forgotten that less than a year and a half after Marie Curie's death (which was from leukemia presumably caused by many years of work with radioactive substances, initially without protective measures), her daughter and son-in-law received the Nobel Prize for the discovery of artificial radiation, increasing the number of Nobel Laureates in one family to four! Her granddaughter presented a lecture at the meeting.

The lectures and poster sessions were held in the Palace of Culture and Science, which is the highest building in Poland (42 stories, 231 m). Completed in 1955, it was a gift of the Stalinist Soviet Union to the Polish People's Republic. The seven scientists who attended the meeting from RERF were quite impressed by the massive building, but found it quite difficult to get oriented and to find one's way around a building which has 3,288 rooms and halls! A well-attended congress plenary lecture was an update on the Fukushima Dai-ichi nuclear power plant disaster by Takeo Ohnishi from the Nara Medical University School of Medicine in Japan. A total of four scientific posters were defended by RERF's **Harry Cullings**, **Kanya Hamasaki**, **Wan-Ling Hsu**, and **Ritsu Sakata**. In addition, **Kazunori Kodama** presented an "Eye-opener" invited lecture "Update on radiation risk estimates from A-bomb survivors," **Kotaro Ozasa** participated in a symposium on biological effects of low doses where he presented an invited lecture on "Radiation risk of cancer and noncancer mortality in atomic-bomb survivors, 1950–2003," and **Evan Douple** participated in a symposium titled "The use of archiving data and biological materials—Examples and strategies," where he presented an invited lecture "The use of unique archived data and biological samples by the Radiation Effects Research Foundation." The large congress provided an excellent opportunity to attend many informative lectures, to promote RERF's latest work and findings, and to meet and exchange information with scientists from many countries.

The long trip home for some of the RERF scientists became longer when they were delayed for two days in Helsinki, Finland, because a typhoon was causing flights to be cancelled in Japan. Their journey should be much shorter in four years when the 15th ICRR returns to Kyoto, Japan, where RERF Board of Councilors member, **Ohtsura**

Dr. Harry Cullings (left) makes a point at his poster with an ICRR participant

Niwa, who was also the 2011 President of the Council of the International Association for Radiation Research, will play a key role in organizing this important event.

Visit to RERF by Dr. Salerno of the National Academies

Evan B. Douple, Associate Chief of Research

On September 14, **Dr. Judith A. Salerno**, the Executive Officer of the Institute of Medicine (IOM) of the National Academies, visited RERF and participated in a workshop related to the RERF studies associated with aging. Dr. Salerno is the executive director and chief operating officer of the IOM and is responsible for managing the IOM's research programs and guiding their work on a daily basis. Prior to coming to the IOM, Dr. Salerno was Deputy Director of the National Institute on Aging (NIA) at the National Institutes of Health, U.S. Department of Health and Human Services. She oversaw aging research conducted and supported annually by the NIA, including research on Alzheimer's and other neurodegenerative diseases, frailty and function in late life, and the social, behavioral and demographic aspects of aging. As the NIA's senior geriatrician, Dr. Salerno was vitally interested in improving the health and well-being of older persons, and designed award-winning programs to communicate health and research advances to the public. She was accompanied in her visit by **Dr. Warren R. Muir**, the Executive Director of the National Academies' Division of Earth and Life Studies, which is the division responsible for supporting RERF using funds from an award from the Department of Energy. Dr. Salerno visited RERF to learn about RERF's research and to provide advice regarding how the research might be of even greater benefit to the problems facing the world's aged populations.

The workshop began with an overview of RERF research by Vice Chairman **Dr. Roy E. Shore**, including historical background, origin and composition of the major cohorts, and a description of the types of research conducted by RERF's departments and working groups. An overview of past and current RERF aging research in the Clinical Studies Department was presented by Department Chief **Dr. Saeko Fujiwara**. The studies using longitudinal Adult Health Study (AHS) data included changes in typical clinical measurements (cholesterol, blood pressure, Hb, and white blood cells), predictors of mortality (biological scores and hand grip), and specific diseases such as stroke (risk factors and lifetime risk). In addition, there have been studies of osteoporosis, dementia, predictors of functional decline, and other aging studies. She described the valuable and extensive laboratory data that has resulted from the physiological tests conducted by the biennial AHS examinations. Lifestyle and medical history data are available on smoking, alcohol consumption, gynecological history, physical activity, diet, and education. Some examples of special studies related to aging included measurement of grip strength, auditory acuity, vibration perception, skin elasticity, and reaction time. Ongoing studies include the development of predictive measures for disability in a national collaborative study, a comparison of body composition (percent fat and percent lean body mass) between AHS participants and a U.S. population (in collaboration with Dr. T. Harris, at the U.S. NIA), and a study of physiological and serum markers for cardiovascular disease or atherosclerosis. All of those studies have both a radiation and an aging component.

Dr. Michiko Yamada continued the workshop by describing the AHS longitudinal data analyses, especially focusing on aging-related disease morbidity, cognitive function and dementia. She emphasized that the large scale of the AHS, the inclusion of both sexes with a broad range of ages, and the long follow-up period allow unique assessment of morbidity of noncancer diseases and trends in measurements with age. Future analyses will include endpoints such as hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, hypothyroidism, and osteo-arthritis. She then turned her attention to dementia, pointing out that RERF has published manuscripts regarding prevalence and incidence of dementia. In responding to questions from Dr. Salerno, Dr. Yamada explained the diagnostic criteria that have been used in the dementia studies and RERF's involvement in the Ni-Hon-Sea collaborative study of dementia using standardized procedures to compare Japanese-Americans living in Seattle and Honolulu with Japanese (Nippon) living in Hiroshima (the AHS cohort). New research studies were begun in 2011 of the A-bomb survivors exposed prenatally or in childhood to assess longitudinal declines in neurocognitive abilities

related to aging and radiation.

Dr. Masazumi Akahoshi, Chief of the Clinical Studies Department in Nagasaki, described results of studies relating aging processes, menopause, diabetes mellitus, and subclinical hypothyroidism. Additional studies have been conducted relating trends in systolic blood pressure and body mass index. He described future study plans, such as measuring body weight fluctuations and aging-related diseases, searching for biomarker differences between obese subjects who do develop diabetes and those who do not, and additional studies of subclinical hypothyroidism and chronic kidney disease.

The workshop then turned to a discussion of the current and potential future aging-related studies using stored biosamples. **Dr. Waka Ohishi**, Assistant Chief of the Clinical Studies Department, Hiroshima, reviewed the varieties and numbers of biosamples whose collection began in 1969 and continues until today based on the AHS or the F_1 clinical cohort, including studies of the role of hormones in breast cancer, the role of *Helicobacter pylori* in gastric cancer, and the roles of hepatitis viruses in hepatocellular carcinoma. She stressed that the potential future of RERF's aging-related studies using stored biosamples includes clinical epidemiologic, immunologic, and genomic studies which may lead to new insights regarding susceptibility to both radiation-induced and aging diseases.

The final session of the discussions with Dr. Salerno included basic science presentations from the Department of Radiobiology/Molecular Epidemiology (RME). Department Chief **Dr. Yoichiro Kusunoki** presented an overview of the current studies of immunosenescence in RME and described a large collaborative project that is continuing to study the effects of both aging and radiation that have been found in the A-bomb survivors. Two major areas of proposed future studies include epigenetic studies of radiation and aging in blood cell subpopulations such as hematopoietic stem cells, dendritic cells, granulocytes, and naïve T cells, and aging-related histological and molecular alterations using autopsy noncancer tissues from the Life Span Study (LSS). **Dr. Kengo Yoshida** discussed potential studies of the decrease in the diversity of T cells and the exhaustion of effector and memory T cells, two hallmarks of immunosenescence, and of epigenomic analyses of memory T-cell populations. The studies should improve our understanding of the role of the changes associated with aging and their resulting impact on cancer and susceptibility to other diseases. **Dr. Yasuharu Niwa** described RERF's study of the radiation effects on aging-related epigenetic changes in various blood cell subsets and of the role of epigenetic changes in aging-related disease among A-bomb survivors. Future studies are planned to explore aging-related epigenetic alterations that may be affected by past radiation exposure, including DNA methylation status of selected genes, genome-wide DNA methylation and histone methylation and acetylation. Also of interest are aging-related mitochondrial dysfunctions in autopsy cardiomyocyte specimens related to methylation and gene expression. **Dr. Reiko Ito** described morphological studies on aging using noncancerous tissues from autopsy samples, such as evaluation of glomerulus number and morphologic changes in the kidney, degeneration of the dermis, and atrophy in the digestive tract. **Dr. Masataka Taga** described studies of radiation effects on noncancer lung tissues among A-bomb survivors with a focus on their roles in carcinogenesis. Since radiation exposure at older ages confers greater lung cancer risk than it does at younger ages, aging-related molecular alterations in lung tissue are of particular interest

Dr. Salerno was impressed with our "incredible information, databases and biosample resources." She encouraged RERF scientists to consider the many opportunities for research projects and to consider collaborative studies and objectives that can be considered across studies, disciplines, and institutions. For example, she indicated that there is currently considerable interest in the aging research community in pre-diagnostic studies in cognitive research and that there is evidence in the area of psychological health to indicate that late-life depression is different from early-life depression. At the end of the day, it was clear that Dr. Salerno's visit had enabled RERF scientists to consider some new areas in which to improve understanding of the aging process and how that knowledge might improve RERF's assessment of radiation-associated risks of health effects.

Dr. Judith Salerno (center) at the aging workshop held in Hiroshima Laboratory

Generation of Novel and Versatile Recombinant Cell Systems That Detect and Measure Genetic Effects of Radiation*

Asao Noda

Department of Genetics, RERF

*This article is based on the following publication:

Noda A, Hirai Y, Kodama Y, Kretzschmar WW, Hamasaki K, Kusunoki Y, Mitani H, Cullings HM, Nakamura N. Easy detection of GFP-positive mutants following forward mutations at specific gene locus in cultured human cells. *Mutat Res* 721:101–7, 2011. (doi:10.1016/j.mrgentox.2010.12.010)

Introduction

Exposure to ionizing radiation may cause mutations that may have long-lasting effects and they can be produced in both somatic and germ cells. Some fraction of the somatic mutants may clonally expand, accumulate additional mutations, and eventually develop into a tumor. With regard to tumors diagnosed in A-bomb survivors, mutations in typical oncogenes or tumor suppressor genes, such as *Ras, Raf, TP53,* and *RET/PTC*, have been analyzed and the results of such studies have been reported in previous issues of *RERF Update*.[1,2] However, it is not yet clear whether the mutations of such target genes were from the "direct hit" of the radiation or from additional damage incurred later during the propagation of the affected cells. Another model of how somatic mutations might result in cancer development is that there may be a target cell in the tissue. It is also reasonable to assume that every cell that constitutes a tissue or organ does not have the same susceptibility to develop cancer. For example, where the mutant cell originates from and whether it was in a differentiated cell region or from a stem cell niche may also be important.

Mutations occurring in germ cells can be transmitted to offspring. While to date no statistically significant increases in genetic effects have been observed in the children (F_1) conceived by A-bomb survivors after the A-bombs, data are available from a number of animal experiments. However, the mutation frequencies for specific loci are generally very low in those animal studies and much ambiguity exists, particularly in the low-dose range that is relevant to the A-bomb survivors.

For the reasons mentioned above, there is a never-ending debate over the shape of the radiation dose-effect curve regarding low-dose exposures and cancer risk (or somatic mutation risk) or genetic effects (germ cell mutation risk). Although analytical results in the low-dose range have been reported,[3] the view of a "linear relationship without threshold" has not been universally accepted.[4]

We wish to help resolve the problems by developing new experimental systems. We are creating model cells and model animals in an effort to efficiently measure the effects of low-dose radiation exposure and to obtain locational information regarding the mutated cells in tissues. Our ultimate goal is to develop an animal model in which living cells fluoresce when mutations arise, in order to accurately measure genetic effects of radiation exposure, to quantify radiation-induced mutation frequencies, and identify the locations of target cells for tumor development. In this article, a cultured cell model will be described as the first step in achieving our goal.[5]

Methods and Results

By applying the regulatory systems of the tetracycline gene expression system in E. coli (T-Rex System, Invitrogen) to mammalian cells, we have created a system in which mutant cells become green, because expression of green fluorescent protein (GFP) is induced when a target gene is mutated (functionally destroyed). The following is an outline of the system. Tetracycline repressor (*TetR*) gene is inserted into the human *HPRT* gene locus to create a cell that can express *TetR* constitutively. Subsequently, we introduce into the same cell a system in which the *GFP* gene is expressed by tetracycline operator (*TetO*). So long as TetR protein is expressed in this cell, *GFP* will not be expressed from *TetO*. However, when a mutation is caused in the *HPRT* gene locus carrying *TetR*, the supply of TetR will halt and GFP protein will be expressed, causing the cell to fluoresce green (Figure 1). Please refer to the original paper and its Appendix,

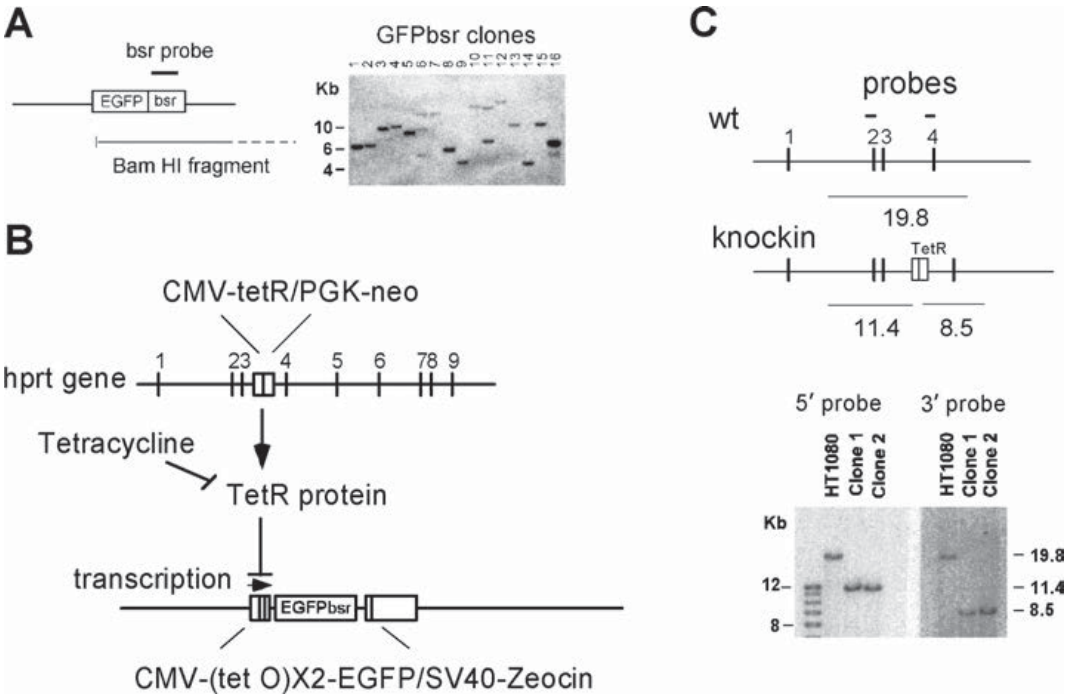


Figure 1. Generation of GFP transgenic/TetR knock-in HT1080 cells

(A) Integration of a single copy of a vector carrying the TetO-EGFPbsr sequence. The left picture indicates locations of the bsr probe and *Bam*HI site, and the right panel shows the results of Southern blots of 16 transfectants.

(B) Diagram illustrating the intracellular system in which GFP transcription is induced by inactivation of *TetR* gene which was inserted in intron 3 of *HPRT* gene by targeted integration, or by inhibition of TetR protein with tetracycline.

(C) Verification of targeted integration of *TetR* gene. DNA from the candidate clones were digested with *Stu*I and hybridized with 5′ or 3′ probes, respectively. Locations of the probes and fragments to be detected are indicated. In wild-type cells both probes detected the 19.8 Kb band, while in knockin cells 5′ and 3′ probes detected the 11.4 and 8.5 Kb bands, respectively.

since the actual gene-targeting approach is much more complicated.

Naturally, inactivation of TetR protein is caused by a gene mutation. Such inactivation, however, is also transiently possible by adding tetracycline to a culture medium (in this case, although TetR protein continues to be produced in a cell, TetR becomes inactive by its binding with tetracycline [allosteric inhibition]). In other words, addition of tetracycline can make a cell fluoresce as a pseudo-mutant cell, as depicted in Figure 2. Such cells turned bright green overnight after being treated with tetracycline (fluorescence intensity of GFP in the cells was at least 200 times greater than that of control cells; Figure 2A). With this level of intensity, it is possible to detect mutant cells readily under a fluorescent microscope (Figure 2B) or by flow cytometer (Figure 2A). Even a mutated cell occurring at a frequency of one per one million can be detected in one to two minutes. While most of naturally-occurring spontaneous mutations are point mutations caused by replication errors of chromosomes in S phase (misreading of DNA polymerase), many radiation-induced mutations are said to be due to the loss of DNA base sequences (wide regions encompassing dozens of Kb). In fact, fluorescent cells appearing after irradiation (mutants) included spontaneous mutations and mutations attributable to radiation injury (Figure 2C). In mutants assumed to be attributable to radiation exposure in particular, the *HPRT* gene locus itself (encompassing at least 40 Kb) is lost.

The frequency of occurrence of spontaneous and radiation-induced mutations was analyzed with the model cells. Cells carry a certain risk of spontaneous mutation. That risk, representing mutability of ordinal cells, namely, genetic stability, is called the spontaneous mutation rate (p). After approximately 20 cell-division cycles, one cell can create a population of 2^{20} or about 10^6 (one million) cells. The number of mutant cells we expect in that cell population simply depends on a probability event (p), related to when the mutant appears during the expansion of the proliferating cell population. If

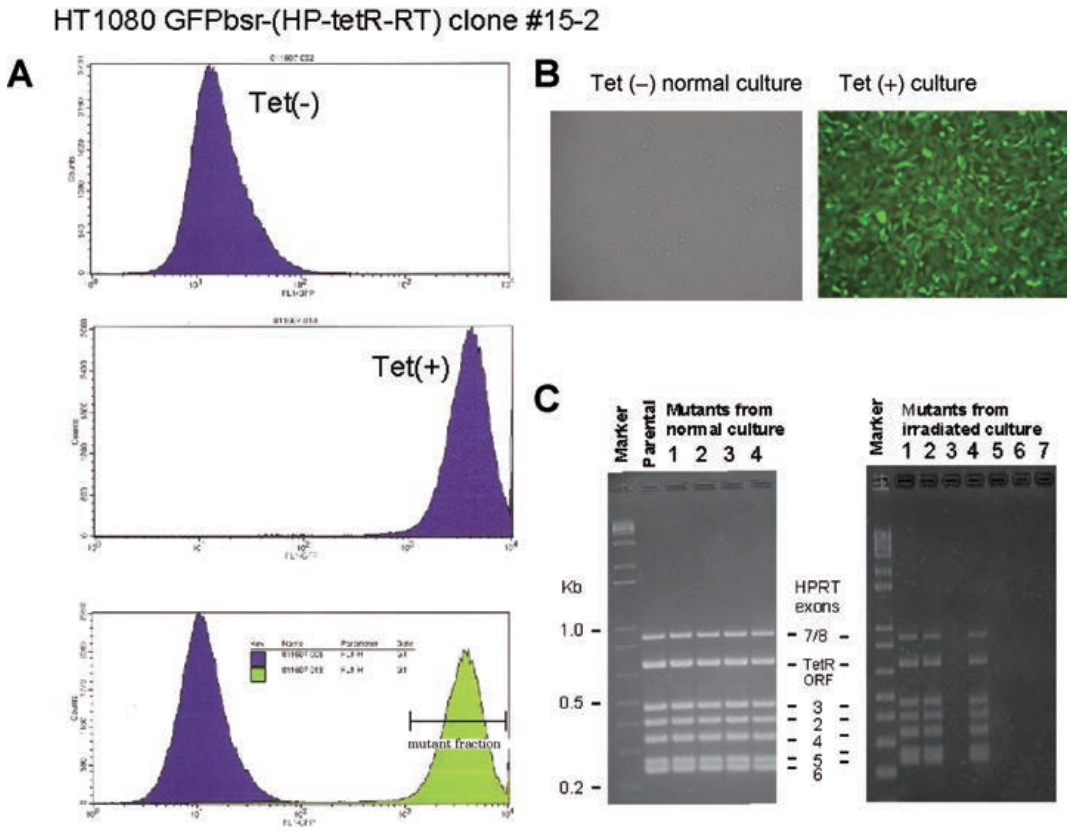


Figure 2. Tet On/Off system verifications and analyses of spontaneous and radiation-related mutants
(A) Flow cytometric analyses of HT1080 cells bearing the TetR/TetO-GFP system cultured overnight in the absence [Tet(–), upper panel] or presence of tetracycline [Tet(+), middle panel]. The lower panel indicates the window for mutant detection (the mean fluorescent intensity is >250-fold higher than in normal cells).
(B) Two representative views under fluorescent microscopy (X100).
(C) Molecular analyses of mutant clones for the presence or absence of *HPRT* exons and *TetR* gene by multiplex polymerase chain reaction. All spontaneous mutants retained the 8 exons whereas four out of seven mutants recovered after radiation exposure had lost all of them.

mutant cells appear in early stages of clonal expansion, and the mutants continue to divide at the same rate as other cells, the apparent mutation frequency will naturally be high. In contrast, if the mutation occurs at the last cell division in the forming of a cell population, the apparent mutation frequency will be very low. Therefore, even if the mutation rate (p) is constant, the apparent mutant frequency will significantly vary depending on when the random event occurs. Although it is possible to use the classical Luria-Delbrück fluctuation test to calculate spontaneous mutation rate (p) of given cells, we have developed a formula using a new measurement method and its results. This measurement method can be characterized as follows: A large cell population (about 5×10^6–10^7 cells) in which mutant frequency is measured in advance is inoculated onto large culture dishes, cultured for short periods to get through a few cell divisions (population doublings), and then cell numbers reached are counted. By obtaining the mutant frequency in this population, mutation rate (p) can be derived. The following is the formula:

$$Mf_1 - Mf_0 = \left[p(n_0 \times 2^{a-1})a/(n_0 \times 2^{a-1}) \right] = pa$$

where Mf_0 and Mf_1 are the mutation frequencies at the beginning and end of the culture process, respectively, n_0 is the number of cells at the time of seeding, and a is the number of cell divisions that took place during the culture (population doublings). After the seeding of 4×10^6 cells, all of the cells were collected every 3–4 days to measure mutation frequency. This process was repeated, with the results shown in Figure 3A. Based on Figure 3A and the above formula, the spontaneous mutation rate (p) of these cells was calculated to be 3.4×10^{-5}/cell division (meaning that mutations occur at a rate of 3.4×10^{-5} per cell division.). Figure 3B shows the dose-response curve regarding radiation-induced mutation. The graph suggests a linear-quadratic curve, with indication of a linear trend in the low-dose ranges. The doubling dose was about 1 Gy.

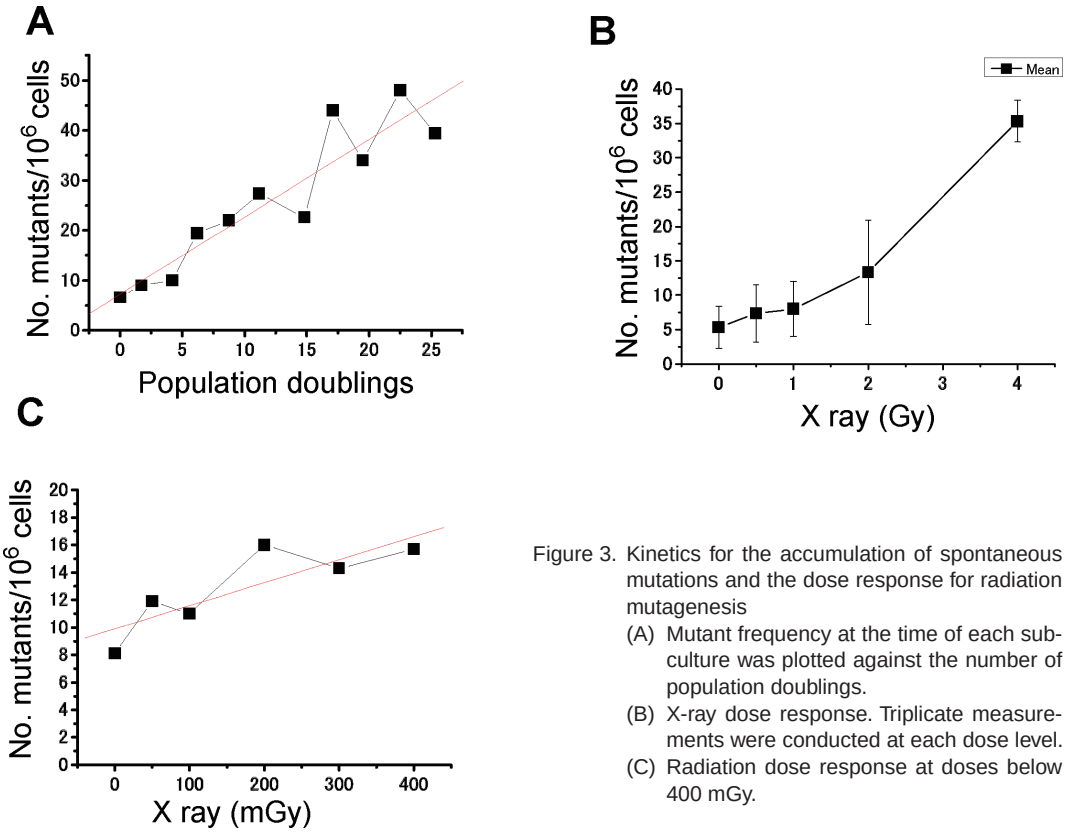


Figure 3. Kinetics for the accumulation of spontaneous mutations and the dose response for radiation mutagenesis
(A) Mutant frequency at the time of each subculture was plotted against the number of population doublings.
(B) X-ray dose response. Triplicate measurements were conducted at each dose level.
(C) Radiation dose response at doses below 400 mGy.

Discussion

We have developed a new cell system characterized by the ability to detect a wide range of mutations, from point mutations involving base substitution to megabase (Mb)-level deletions. It is therefore possible to measure not only mutagenic effects of radiation, but also of other kinds of chemical and environmental mutagens. In order to detect the number of mutants, conventional methods require colony formation of mutant cells, a large number of culture dishes, and culturing over many days. Our system only requires direct counting of the individual mutant cells for calculating mutant frequency. Since it is possible to insert *TetR* gene into any region of a chromosome (targeted integration) with this method, it should become possible to measure radiation-induced mutation frequency in any important gene. Furthermore, the next step is the creation of a system to measure genetic effects (somatic mutations as well as germ cell mutations) of radiation in all the cells in the entire body of a mouse. We hope that our proposed model animal will allow accurate measurement of genetic effects of low-dose radiation and detection of radiation-induced mutation of target cells susceptible to carcinogenesis, and thereby provide supplementary data for use in RERF's research.

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Effects of Radiation Exposure and Hepatitis Virus Infection on Risk of Hepatocellular Carcinoma among Atomic Bomb Survivors*

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are recognized as critically important risk factors for HCC. However, an increase of non-B, non-C HCC without HBV and HCV infection has been noted recently in Japan.[1,2] The etiology of non-B, non-C HCC has been poorly understood, though alcoholic hepatitis, nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH), and hemochromatosis[3,4] are known as risk factors. In Japan, NAFLD has increased along with Westernization of lifestyle, and most NASH cases have developed due to such lifestyle-related diseases as obesity, diabetes mellitus, and hyperlipidemia.[5] Obesity and diabetes mellitus, as well as NAFLD, have also recently received increased attention as risk factors for HCC.[6–12]

An increased risk of liver cancer with radiation dose among atomic bomb survivors has been reported based on tumor registries, mortality studies, and pathology review,[13–16] but hepatitis virus infection status has not been taken into account. On the other hand, the cohort study in workers at the Mayak nuclear facility demonstrated that the risk of liver cancer mortality was significantly associated with plutonium exposure,[17] and that the incidence of HCC was marginally significantly associated with plutonium exposure.[18] However, liver cancer in those analyses included hepatoblastoma and intrahepatic cholangiocarcinoma as well as HCC. In addition, hepatitis virus infection status was not taken into account in a strict and in-depth manner, though HCC accounted for most of the liver cancer.

With the aim of determining whether radiation exposure is an independent risk factor for HCC, even after adjusting for hepatitis virus infection, alcohol consumption, BMI, and smoking habits, we conducted a nested case-control study among atomic bomb survivors using stored sera. We also evaluated whether radiation, alcohol consumption, increase in body mass index (BMI), and smoking habit contribute to increased risk for non-B, non-C HCC.

Materials and Methods

Cohorts. The Atomic Bomb Casualty Commission (ABCC) and its successor, RERF, established the Adult Health Study (AHS) longitudinal cohort in 1958, in which more than 20,000 gender-, age-, and city-matched proximal and distal atomic bomb survivors and persons not present in the cities at the time of bombings are examined biennially in outpatient clinics in Hiroshima and Nagasaki.

Cases and controls. Incident cancer cases were identified through the Hiroshima Tumor and Tissue Registry and Nagasaki Cancer Registry, supplemented by additional cases detected via pathological review of related diseases.[19] As described in our previous study,[6] 359 primary HCC cases were diagnosed among 18,660 AHS participants between 1970 and 2002, who visited our outpatient clinics before their diagnosis. Of those, 229 cases had serum samples obtained within six years before HCC diagnosis. After excluding five cases with inadequate stored serum, 224 cases remained for our study.

Three control sera per case were selected from the at-risk cohort members matched on gender, age, city, and time and method of serum storage, and countermatched on radiation dose in nested case-control fashion.[20] Countermatching (to increase statistical efficiency for studying joint effects of radiation and other factors) was performed using four strata based on whole-body (skin) dose.

Laboratory tests. HBsAg and antibody to hepatitis B core antigen (anti-HBc Ab) were measured by enzyme immunoassay (EIA), and anti-HCV Ab was measured by second-generation EIA as previously described.[21,22] Qualitative detection of HCV RNA among anti-HCV-positive samples was performed based on the nested polymerase chain reaction (PCR) method, as previously described.[22] HBV infection (HBV+) status was defined as positive for HBsAg or having a high titer of anti-HBc Ab. HCV infection (HCV+) status was defined as positive for HCV RNA. Non-B, non-C status was defined as negative for HBsAg and not having a high titer of anti-HBc Ab (HBV–) as well as negative for HCV RNA (HCV–).

Radiation dose. Radiation dose to the liver was estimated for each subject according to Dosimetry System DS02.[23] A weighted sum of the gamma dose in gray plus 10 times the neutron dose in gray was used.

Information on alcohol consumption, BMI, and smoking habit. Information on alcohol consumption was obtained from the 1965 AHS questionnaire when available, with missing data complemented using the 1978 mail survey. Alcohol consumption was quantified as volume of each type of alcoholic beverage; mean ethanol amounts were calculated as grams per day as previously described.[24] BMI (kg/m^2) was calculated from height and weight measured at the AHS examination. Information on smoking habit was obtained from the 1965 questionnaire; subjects were categorized as never, current (at time of survey), or former smoker.

Ethical consideration. This study (RERF Research Protocol 1-04) was reviewed and approved by the Research Protocol Review Committee and the Human Investigation Committee of RERF.

Statistical analyses. The nested case-control design is analyzed using a partial likelihood method analogous to that used for cohort follow-up studies,[25] which is in practice the same as the conditional binary data likelihood for matched case-control studies[26] except that the subjects (cases and "controls") in the study are not completely independent due to repeated selection. Cumulative incidence of HCC by follow-up time (year) and age was derived according to the method of Nelson and Aalen, using Cox regression to adjust for age at start of follow-up. Cumulative incidence by radiation dose groups (0–0.0009, 0.001–0.999, and 1.0+ Gray) was compared using the Gehan/Breslow generalized Wilcoxon test. All factors other than radiation were analyzed using relative risks (RRs) estimated by a log-linear model. Although radiation exposure could have been adjusted by matching on radiation dose as an additional matching factor in the control selection,[27] in addition to assessing effects of lifestyle factors and viral hepatitis, another purpose of the present study was to examine effects of radiation exposure after adjustment for possible confounding and interaction by these factors, so matching on radiation—which precludes analysis of radiation risk—was not desirable; rather, we countermatched on radiation.[20,25,28] Radiation risk was analyzed using an excess relative risk (ERR) model (ERR = RR – 1) as has been done previously.[29]

Results

Characteristics of cases and controls. HCC cases and controls were comparable with respect to gender, age, city, and time and method of serum storage by design. Prevalence of HBV and/or HCV

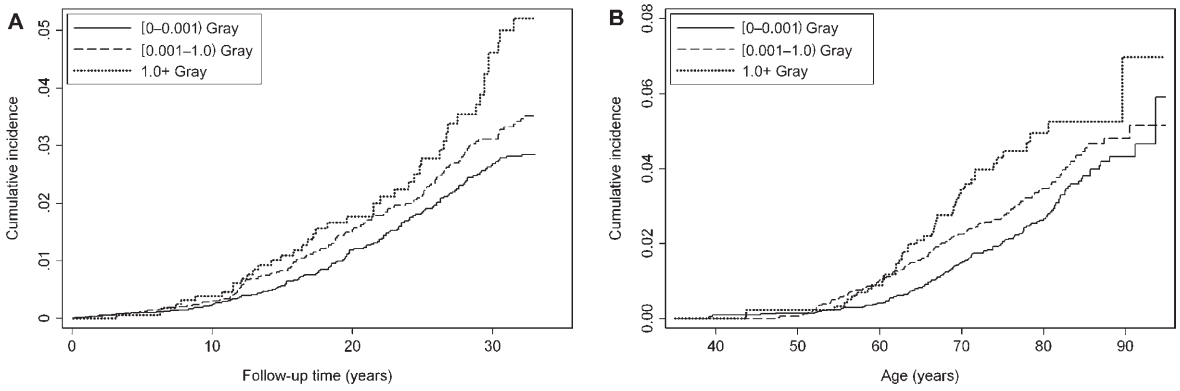

Figure. Cumulative incidence of HCC (1970–2002) by radiation dose
Dotted line = radiation dose ≥1.0 Gy; dashed line = radiation dose 0.001 ≤ <1.0 Gy; solid line = radiation dose 0 ≤ <0.001 Gy. Cumulative HCC incidence by follow-up time (A) and age (B) increased significantly (P = 0.028, P = 0.0003, respectively) with radiation dose.

infection status in HCC cases is higher than those in controls. Higher proportions of HCC cases had a history of alcohol consumption of more than 40 g of ethanol per day, were obese (BMI >25.0 kg/m^2), and were current smokers, compared with the controls. HCC cases also received on average higher radiation doses to the liver, compared with the controls.

Cumulative incidence of HCC by radiation dose. Figures A and B show the cumulative incidence of HCC by radiation dose using either follow-up time (adjusted for age at start of follow-up) or age. Of 359 HCC cases diagnosed among 18,660 AHS subjects between 1970 and 2002, the analysis was performed using 322 HCC cases, based on 16,766 subjects with known radiation dose. A significant increase with radiation dose was seen with cumulative incidence both by follow-up time (P = 0.028) (Figure A) and by age (P = 0.0003) (Figure B). The effect of radiation was especially evident at age 60 years or later.

Risk of HCC for radiation and hepatitis virus infection. After adjustment for categorical alcohol consumption, BMI, and smoking habit, a significant association was found between HCC and radiation dose or hepatitis virus infection, resulting in an RR at 1 Gy of 1.67 (95% confidence interval [CI], 1.22–2.35, P < 0.001) for radiation and RRs of 63 (95% CI, 20–241, P < 0.001) for HBV+/HCV– status and 83 (95% CI, 36–231, P < 0.001) for HBV–/HCV+ status. The above estimates changed little when radiation and hepatitis virus infection were fit simultaneously (Table 1).

Risk of HCC for radiation after excluding persons with either or both hepatitis virus infections. The adjusted analyses indicated that radiation exposure was significantly associated with increased risks for HCC, even after excluding HBV- or HCV-infected individuals. Furthermore, significant association was found between non-B, non-C HCC and radiation dose, resulting in RR at 1 Gy of 1.90 (95% CI, 1.02–3.92, P = 0.041) for radiation without adjustment for categorical alcohol consumption, BMI, and smoking habit and 2.74 (95% CI, 1.26–7.04, P = 0.007) with such adjustment (Table 2).

Risk of non-B, non-C HCC. Effects of alcohol consumption, BMI, and smoking habit on non-B, non-C HCC risk with or without adjustment for radiation dose were estimated using continuous and categorical covariates. Risk of non-B, non-C HCC for alcohol consumption per 20 g of ethanol per day was significant with a log-linear model (adjusted RR 1.64, 95% CI, 1.05–2.81, P = 0.029), but was limited to the category ≥40 g of ethanol per day (adjusted RR 5.49, 95% CI, 0.98–39.2, P = 0.052). Significant log-linear association was not found with continuous BMI, and even the category BMI >25.0 kg/m^2 10 years before diagnosis did not evidence significant risk despite a rather large estimate of RR (adjusted RR 3.17, 95% CI, 0.92–12.3, P = 0.068). Current smoking evidenced significant

Table 1. Risk of HCC for radiation and HBV or HCV infection status

Variables	Number of Cases/Controls	Unadjusted RR (95% CI)		Adjusted* RR (95% CI)	
		Alone†	Joint‡	Alone†	Joint‡
Radiation (at 1 Gy)	186/600	1.40 (1.07–1.89)	1.39 (0.93–2.26)	1.67 (1.22–2.35)	1.82 (1.09–3.34)
HBV+/HCV–	24/14	34 (13–106)	30 (11–91)	63 (20–241)	50 (16–184)
HBV–/HCV+	119/35	57 (27–140)	58 (28–147)	83 (36–231)	87 (37–251)

Abbreviations: CI, confidence interval; RR, relative risk
* Adjusted for categorical alcohol consumption, BMI 10 years before diagnosis, and smoking habit.
† Radiation dose to the liver and hepatitis virus infection status were fit separately.
‡ Radiation dose to the liver and hepatitis virus infection status were fit simultaneously.

Table 2. Risk of HCC for radiation after excluding persons infected with HBV and/or HCV

Subjects	Number of Cases/Controls	Unadjusted	Adjusted*
		RR at 1 Gy (95% CI)	RR at 1 Gy (95% CI)
Exclude HBV+ (no HCV adjustment)	161/452	1.48 (1.10–2.05)	1.91 (1.34–2.81)
(adjust for HCV)		1.60 (0.997–2.78)	2.32 (1.25–4.76)
Exclude HCV+ (no HBV adjustment)	66/176	1.61 (1.003–2.76)	1.91 (1.13–3.48)
(adjust for HBV)		1.68 (0.96–3.23)	2.16 (1.12–4.76)
Exclude both HBV+ and HCV+†	42/108	1.90 (1.02–3.92)	2.74 (1.26–7.04)

Abbreviations: CI, confidence interval; RR, relative risk
* Adjusted for categorical alcohol consumption, BMI 10 years before diagnosis, and smoking habit.
† Non-B, non-C status

risk (adjusted RR 5.95, 95% CI, 1.34–33.2, P = 0.018), but there were no continuous data on amount smoked.

Discussion

The present study confirmed that radiation is associated with increased incidence of HCC among atomic bomb survivors. Additionally the nested case-control study indicates that radiation and HBV and HCV infection are associated with increased risk for HCC, and that radiation remains an independent risk factor for HCC after taking into account hepatitis virus infection, alcohol consumption, BMI 10 years before HCC diagnosis, and smoking habit. Furthermore, significant association was observed between non-B, non-C HCC and radiation dose, alcohol consumption, and smoking, while obesity 10 years before diagnosis was marginally significantly associated with increased risk for non-B, non-C HCC.

In the analysis (Table 1) in which radiation dose and hepatitis virus infection were fitted separately, radiation was significantly associated with increased risk for HCC with or without adjustment for alcohol consumption, BMI, and smoking habit. Although this finding is in agreement with our previous understanding that liver cancer risk is significantly associated with radiation without adjustment for hepatitis virus infection among atomic bomb survivors, it is difficult to compare the HCC risk estimates between the previous and current study results.[13–16] The difficulty is caused by the inclusion of hepatoblastoma and intrahepatic cholangiocarcinoma in addition to HCC as liver cancer cases in analyses of tumor registry-based liver cancer risk (ERR at 1 Sv = 0.49),[13] mortality study- and tumor registry-based[15,16] liver cancer mortality risk (male: ERR per Sv = 0.39, female: ERR per Sv = 0.35), and liver cancer risk (male: ERR per Gy = 0.32, female: ERR per Gy = 0.28), despite the fact that the majority of liver cancer cases were HCC. Because a relatively large fraction of liver cancer cases was included that were diagnosed only on the basis of death certificates,[13,16] complete exclusion of metastatic liver tumor cases from such cases may not have been possible. Metastatic liver tumor cases were excluded in an analysis of pathological review-based liver cancer risk (ERR per Gy = 0.81), but hepatoblastoma and intrahepatic cholangiocarcinoma were included with HCC.[14]

In the current analyses adjusted for alcohol consumption, BMI, and smoking habit, the RR estimates for radiation increased slightly and showed statistical significance with adjustment for HBV and HCV infection status. HBV infection may be considered an intermediate risk factor for HCC, because three of four previous HBV screenings demonstrated that HBsAg prevalence increases with radiation dose;[30–33] therefore, adjustment for HBV infection status might be expected to result in a decreased radiation risk estimate. However, such interpretation is difficult because the risk estimate was also adjusted for HCV infection status, although anti-HCV Ab prevalence is not significantly associated with radiation dose.[34] We therefore examined HBV and HCV infection status and concomitant radiation effects separately, excluding persons with one or the other viral infection.

RRs of HCC for radiation after excluding persons infected with HBV or HCV were generally higher than with the full data, but differed little depending on which virus was used for exclusion (Table 2). As with the full data, adjustment for HBV or HCV infection status reduced the statistical significance of the radiation effect but had little impact on the RR estimates themselves. The RR of HCC for radiation after excluding persons infected with HBV and HCV (i.e., the RR of non-B, non-C HCC for radiation) was significant with or without adjustment for alcohol consumption, BMI, and smoking habit. As there can be no viral mediation of the radiation risk in non-infected individuals, lower radiation risks estimated in infected individuals might be considered evidence of mediation, but mediation would imply that risk decreases with adjustment for viral infection status, which did not occur. The reduction in statistical significance with adjustment for HBV and HCV infection status might be due to loss of power when further parameters for the risks of HCC for hepatitis virus infection are estimated or the number of subjects is reduced by exclusion.

In conclusion, radiation exposure was associated with increased risk of HCC, even after adjusting for HBV or HCV infection, alcohol consumption, BMI, and smoking habit. Moreover, radiation exposure was an independent risk factor for non-B, non-C HCC with no apparent confounding by alcohol consumption, BMI, or smoking habit. The mechanistic form of joint effects of radiation and HBV or HCV infection on HCC risk could not be estimated, but the development of new statistical methods that jointly consider the dose response for the intermediate viral factor will make such an analysis possible in the future. In particular, in-depth understanding of the mechanisms by which radiation exposure as well as obesity, alcohol drinking, and smoking contribute to development of non-B, non-C HCC may lead to prevention, early detection, and better therapeutic strategies.

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Lifetime Risk of Stroke and Impact of Hypertension: Estimates from the Adult Health Study in Hiroshima and Nagasaki*

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Takahashi I, Geyer SM, Nishi N, Ohshita T, Takahashi T, Akahoshi M, Fujiwara S, Kodama K, Matsumoto M. Lifetime risk of stroke and impact of hypertension: Estimates from the Adult Health Study in Hiroshima and Nagasaki. *Hypertens Res* 34:649–54, 2011. (doi:10.1038/hr.2011.7)

Introduction

With the aging of Japan's population, stroke has become an ever more important health burden, and thus activities aimed at stroke prevention require urgent attention. While elevated blood pressure (BP) has emerged as one of the prominent risk factors for stroke, when to start treatment of hypertension and what levels of hypertension require medication remain undetermined issues. In particular, a point of great debate is whether prehypertension conditions signify a risk of stroke.

It has been suggested that competing events in non-stroke death may cause bias in risk estimates of stroke based on longitudinal observations.[1] The aim of our study is to clarify the importance of hypertension management for the purpose of risk prevention, by calculating the association between lifetime risk (LTR) of stroke with consideration of competing risks and several baseline age BP categories.

Methods

This study was comprised of some of the RERF's Adult Health Study (Hiroshima, Nagasaki) participants, who have been followed through biennial health examinations over a period of more than 50 years (20,000 subjects in 1958, the start of follow-up; follow-up rate 100%; participation rate for health exams over 70%). We calculated LTR of stroke for various blood pressure-based groups among 7,847 subjects who had no history of stroke before the baseline ages of 55 years or younger and who underwent blood pressure measurements between the ages of 55 and 56, using cumulative incidence analysis and adjusting for competing risks. The observation period was 1958–2003. First-ever stroke cases were identified by clinical records, death certificates, and autopsy records in accordance with the definitions in the World Health Organization (WHO)-initiated Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project. Analyses of LTR of stroke in the various baseline-age cohorts of 45, 55, 65, and 75 years were carried out after adjustment was made for competing risk of non-stroke death. BP groups were defined in accordance with criteria from the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7): normal, <120/80 mmHg; prehypertension, 120–139/80–89 mmHg; stage 1 hypertension, 140–159/90–99 mmHg; and stage 2 hypertension, ≥160/100 mmHg.

Results

The Table indicates characteristics of the 7,487 subjects, who were observed from the baseline age

Table. Characteristics at the baseline age of 55 years

Men			
Blood pressure	Normal	[%]	20.0
	Prehypertension		34.5
	Stage 1 hypertension		26.4
	Stage 2 hypertension		19.1
Body mass index (median)		[kg/m^2]	21.8
Total cholesterol (median)		[mg/dl]	179
Women			
Blood pressure	Normal	[%]	27.0
	Prehypertension		34.9
	Stage 1 hypertension		22.3
	Stage 2 hypertension		15.7
Body mass index (median)		[kg/m^2]	22.6
Total cholesterol (median)		[mg/dl]	199

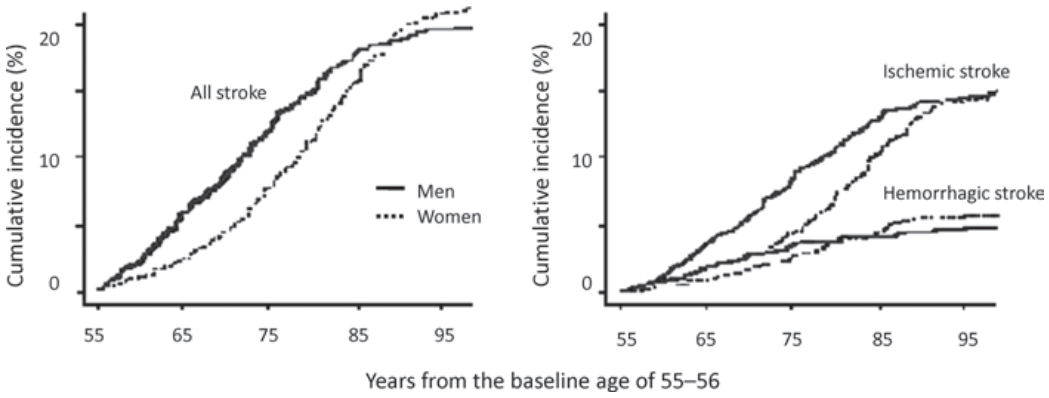

Figure 1. Cumulative incidence, accounting for competing risk

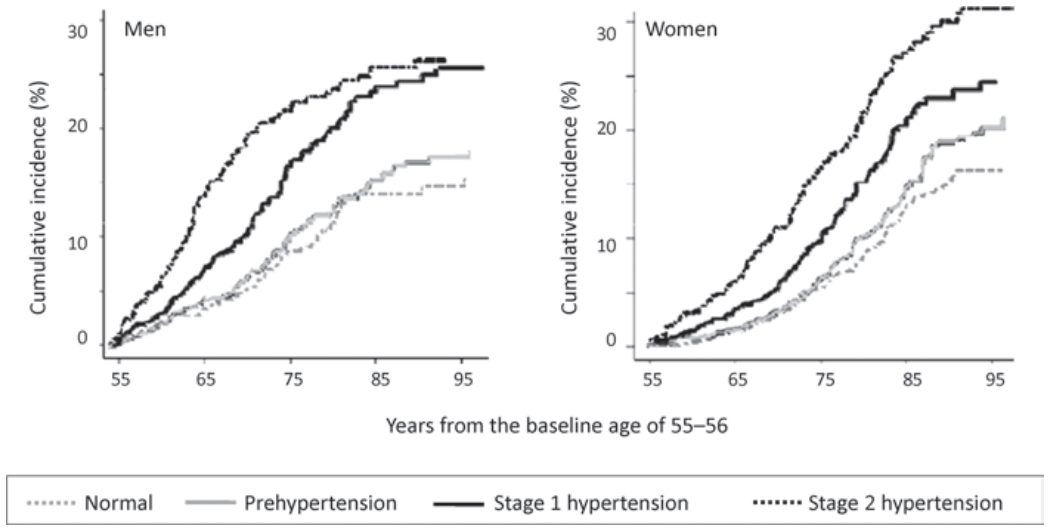

Figure 2. Cumulative incidence of all stroke by blood pressure group

of 55 years. LTR of all stroke was 20.5% in men and 22.2% in women (Figure 1). Female LTR was slightly higher than male LTR. BP was a significant factor in determining risk of stroke for men and women, with distributions of cumulative risk for stroke significantly different across BP groups (Figure 2). Separated into ischemic/hemorrhagic strokes, results followed the same pattern. For men, LTR of ischemic stroke for normotension, prehypertension, stage-1 hypertension, and stage-2 hypertension was 11.2, 10.7, 18.3, and 17.3%, respectively, while LTR of hemorrhagic stroke was 1.5, 4.2, 5.4, and 6.4%. For women, LTR of ischemic stroke was 11.3, 13.1, 14.5, and 18.4%, respectively, while LTR of hemorrhagic stroke was 3.7, 4.7, 6.2, and 8.9%. The estimates did not differ significantly among any of the baseline ages of 45, 55, 65, and 75 years.

Discussion

Few reports have been published on LTR of stroke: one each from the United States (the Framingham Study),[1] Holland (the Rotterdam Study),[2] and Japan (the Suita Study).[3] Ours is the first report to investigate the relationship between LTR of stroke and BP at each baseline age. LTR of all-stroke in our study was similar to the reported results from the previous studies. Our longitudinal study using LTR estimates indicated that hypertension in midlife remained a risk factor for stroke compared with normotensive subjects. Regarding the controversial issue of impact from prehypertension (120–139/80–89 mmHg) on stroke events, our results did not indicate significant risk of stroke in that category.

Conclusion

Our study suggests that hypertension at midlife among Japanese subjects affects LTR for stroke. It is therefore important to address this risk early on, when hypertension is first diagnosed to ensure that effective therapy can be initiated and stroke risk is lowered.

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Unveiling Ceremony of Monument Honoring Barbara Reynolds

A monument honoring Ms. Barbara Reynolds, a U.S. peace activist who protested against nuclear arms all over the world together with Hiroshima's A-bomb survivors, was erected in the Hiroshima Peace Memorial Park. The unveiling ceremony on June 12, 2011 was organized by the World Friendship Center, an organization Ms. Raynolds worked hard to establish, and attended by about 110 individuals including Barbara's family members and A-bomb survivors who joined her in peace and anti-nuclear activities.

Barbara first came to Japan in 1951 accompanying her husband Earle Reynolds who worked at the Atomic Bomb Casualty Commission (ABCC), RERF's predecessor. Shocked by the devastation caused by the atomic bomb, she continued her appeal for peace and abolition of nuclear weapons, traveling on peace pilgrimages and conducting other activities, with A-bomb survivors. At the end of their voyage in 1960 as they pulled into Hiroshima's harbor, they were greeted as heroes. People thanked them for telling the world what happened in Hiroshima and for sailing into the restricted zone in an attempt to stop the testing of nuclear bombs in the Marshall Islands. In 1975, she was named a special honorary citizen of Hiroshima. The words she often spoke "I, too, am a hibakusha" are inscribed on the monument.

RERF Chairman Toshiteru Okubo made an address at the unveiling ceremony, followed by speeches from Hiroshima Mayor Kazumi Matsui, Hiroshima Municipal Assembly President Takashi Kijima, and Hiroshima University Extraordinary Professor Tadatoshi Akiba (former Hiroshima mayor). Following are Dr. Okubo's address and the remarks made by Mrs. Jessica Reynolds Renshaw, Barbara's daughter.

Address made by RERF Chairman Toshiteru Okubo [excerpted]

Dr. Earle Reynolds, who was Barbara's husband and an anthropologist, was assigned to investigate the effects of A-bomb radiation on children at the former Atomic Bomb Casualty Commission (ABCC), presently Radiation Effects Research Foundation (RERF), where I work. Beginning in 1951 he conducted research by studying the children for three years. In 1954 the results of his studies were published in a journal of the Pediatrics Society of Japan.

The RERF has investigated the medical effects of radiation on human health and related diseases. Although this research began as a result of the terrible disaster of the exposure to the A-bomb, it was possible thanks to the understanding and cooperation of many A-bomb survivors and others. Now the result of that research contributes to interpretation of important knowledge for medical care for the radiation-exposed caused by nuclear accidents and medical exposures as well as for A-bomb survivors.

Hibakusha didn't use their tragic experiences for an act of "retaliation." On the contrary, they firmly agreed to use that experience for prayer and a desire for peace. We sympathize with them about this matter from the bottom of our hearts. Barbara, too, must have been strongly moved to desire world peace, for she lived in Hiroshima shortly after the war and saw the hibakusha's way of living.

From now on, as future generations pass in front of this monument near the cenotaph in Peace Memorial Park, I wish they will continue her appeal for the total abolition of nuclear weapons. In conclusion I'd like to thank all of those who continue to follow her will and are devoted to the development of the World Friendship Center. Thank you very much.

Remarks made by Jessica Reynolds Renshaw [excerpted]

Dear Members of the Monument Committee, hibakusha, friends, and family,

We are happy to meet with you today. My husband Jerry and I have come from California and my nephew Tony, one of Barbara's grandsons, has come from Texas. We also represent my brothers, Barbara's sons Tim and Ted Reynolds, and her other eight grandchildren who would have come if possible.

We are here at the invitation of the Dedication Committee to unveil a monument to my mother, who would have been 96 years old today. To me, it is amazing that the hibakusha of the nuclear bomb dropped by Americans would erect a monument to an American woman at their Ground Zero. I am so humbled by your forgiveness and desire to do this. Many people whose lives have been touched by my mother's life call her a saint, even a "national treasure." But my mother would have been the first to say she was just an imperfect human being.

In September, 1964, my mother was 49 years old. Years before, my father had been part of a team sent by the American government to study the effects of radiation on Hiroshima hibakusha—to

draw their blood, measure their height and weight, and so on. But no one had asked them, "What was it like to experience an atomic bomb?" No one had listened to them or cried with them. Now, in obedience to her heavenly Father, my mother went back to Hiroshima, despite her sense of personal shame, to listen to them and serve them, to be God's hands and feet and voice. Out of her humility and obedience bloomed the World Friendship Center.

She was not only a voice from the heavenly Father to the hibakusha. Hibakusha told her they considered her a voice for Hiroshima and Nagasaki to the world. She took that responsibility very seriously. And as she came to know them, they taught her the value of each life. She came to respect the brave, suffering, patient survivors of the first two nuclear bombs dropped on human beings. She began to identify with them and hurt for them. And so she said, "I, too, am a hibakusha." She wanted to accurately convey to the world their message, "No more Hiroshimas!" to urge everyone on the planet to choose peace and prevent the horror and catastrophe of Hiroshima from happening to anyone else, ever.

Since 1945, starting in Hiroshima and Nagasaki, the number of people exposed to the poison of radiation has grown through Chernobyl, Three-Mile Island and now Fukushima. Radiation does not distinguish between war and peace. Radiation from nuclear weapons keeps killing after the war is over. We are here to assure all radiation-exposed people anywhere that we will not forget your distress. We will pass your message on from generation to generation: "No More Hiroshimas!" "No more Nagasakis!" "No more Fukushimas!"

As you unveil this monument, my mother is just a symbol. She is a symbol of love, pointing to the source of love, the heavenly Father. She is a symbol of hope because anyone of us who humbles himself to listen to the "still, small voice" of our Heavenly Father can make a mighty difference. Thank you for honoring my mother in this way.

Dr. Toshiteru Okubo speaks at the monument's unveiling ceremony

(from left) Mr. Jerry Renshaw, Mrs. Jessica Renshaw (Barbara Reynolds' daughter), Mr. Tony Reynolds (Barbara Reynolds' grandson), and Mr. Hiromu Morishita (Chairman of the World Friendship Center)

Report on the Health Examinations for A-bomb Survivors in North America

Akihiko Suyama, Chief
Department of Epidemiology, Nagasaki

It was my third time to join in a medical team for health examinations of A-bomb survivors in North America and, for the first time, I traveled to Los Angeles and Honolulu.

The Los Angeles and Honolulu medical team was headed by Dr. Makoto Matsumura (Permanent Director, Hiroshima Prefectural Medical Association [HPMA]), with Dr. Shizuteru Usui (President, HPMA) as general leader, and consisted of eleven members, namely seven medical doctors including myself and four administrative staff members from HPMA, Hiroshima City/Prefecture, Nagasaki City/Prefecture, and RERF (Mr. Hideo Shinoda). The Seattle and San Francisco medical team was led by Dr. Jitsuro Yanagida (Permanent Director, HPMA), and also consisted of seven medical doctors, including Dr. Yoshimi Tatsukawa (RERF) and four administrative staff members from the aforementioned organizations. Detailed reports from these medical teams are posted on the website of HPMA (*Ishikai Sokuho* No. 2125 and No. 2128; in Japanese).

Since Japanese physicians do not usually have a license to practice medicine in the U.S., we are not allowed to perform such medical procedures as health examinations or explanations of test results. The health examinations by Japanese doctors had been supervised by American physicians with a U.S. medical license, but in Honolulu this time, as a trial attempt, a doctor from Japan together with a U.S. physician licensed by the State of Hawaii jointly performed the examinations.

Professor Jerris Hedges (emergency medical care), Dean of the School of Medicine, the University of Hawaii, and Dr. Fernando V. Ona, a leading specialist in gastroenterology in Honolulu, provided me support on different days. It took me considerable effort to carry out the health examinations, explaining in English the medical records written in Japanese and having Drs. Hedges and Ona perform the examinations from time to time. However, I was able to observe directly how U.S. doctors communicated with and handled examinees in a U.S. examination room. I also had a chance to talk with those experienced medical practitioners about how we would handle suspected disease in consideration of various clinical guidelines in the U.S., and that's where I sometimes noticed slight differences in approaches between the U.S. and Japan.

In addition to the generation of examinees speaking Hiroshima dialect, there were also an increasing number of examinees wanting to undergo the examinations in English. I felt that the aforementioned collaboration with such skillful U.S. doctors in the examinations further enhanced the examinees' confidence in our medical team based on Japanese support for the A-bomb survivors in the U.S. Some examinees, however, still expected to be examined by Japanese doctors like the previous examinations, and it therefore may be time for us to review what is expected from the future medical teams for this North America program.

When I first participated in the North America program in 2005, some examinees in Seattle and San Francisco told me that I was the first doctor from Nagasaki to participate in the health examinations. Receiving such a comment was only natural, since the North America program had been promoted by HPMA. The reality is, however, that many examinees were exposed to the A-bombing in Nagasaki, and I thus perceived their considerable expectation for participation by a physician from Nagasaki. I traveled with medical teams to Seattle and San Francisco in 2005 and 2007, and after returning to Japan, I had several experiences of receiving long-distance telephone calls from the U.S. from the examinees telling me about their returning to Nagasaki for treatment and actually meeting with the examinees in Nagasaki and hearing of their misgivings about treatment in the U.S. I was fortunate to participate in the North America program as a medical team member on the three occasions I indicated above while a physician belonging to the RERF Nagasaki Laboratory, and I feel that my participation in the medical team somewhat contributed to provide a sense of relief to the examinees exposed to the atomic bomb in Nagasaki and now living in North America.

The North America program began in 1977 as a cooperative project between HPMA and RERF. The biennial health examination program was entrusted to Hiroshima Prefecture as a national government program in 2007, and later to HPMA from the prefectural government. RERF collaborated in dispatching doctors and administrative staff members to the program for many years, and

since 2011 handled activities including preparation of a report after the health examinations as work officially entrusted by HPMA.

When I joined the North America program for the first time in 2005, I learned many things from three publications—"Were We the Enemy? American Survivors of Hiroshima (English translation)" by Rinjiro Sodei, and "*Ikinokotta Hitobito* (Survivors)," Volumes I & II (Japanese) by Fuyuko Kamisaka. From Mr. Sodei's book in particular, I learned so much about the history of RERF's involvement in the North America program. Mr. Hiroaki Yamada, a former ABCC employee, put forth great effort in initiating the North America program. Many people have supported the program through various interactions in the four cities of Seattle, San Francisco, Los Angeles, and Honolulu, including the A-bomb survivors, either as groups or individuals, who prepared examinee lists and handled relevant contacting work, hospitals/clinics providing volunteer medical staff, who worked on weekends to support work related to the health examinations and venues, other volunteer groups as friends of A-bomb survivors consisting of non-survivors, and people from associations of Japanese physicians residing in the U.S., among so many others. In terms of making contact with those people, people like Mr. Yamada of ABCC and more recently Mr. Tadaaki Watanabe of RERF had a feeling for the survivors in North America from a humanitarian viewpoint, and made efforts ignoring their own individual sacrifices for the sake of RERF as an organization and occupation, and thus I cannot help but think the efforts made by ABCC and RERF staff ensured that the program has been maintained to this point without losing ties with all those involved.

Chief of Secretariat Midori Mukai of HPMA, who started her involvement with this most recent program, made every effort to maintain the human ties developed so far, and I saw firsthand her preparations in North America for the program.

RERF's future involvement in the North America program will be reviewed on the basis of the results from the latest project. It is my strong desire that the North America program be continued without lapse to the next round of examinations, learning from its legacy built jointly by ABCC-RERF and HPMA since the program's start.

Finally, I was asked to explain the radiation effects from the Fukushima Dai-ichi nuclear power plant crisis, when we visited the Los Angeles county's medical association, Providence Little Company of Mary Medical Center Torrance (venue for the health examinations), and the Japanese Consulate General. Interest in the nuclear crisis in Fukushima was incredibly high in Los Angeles, since there is a nuclear reactor located not very far from the city, and Los Angeles is in a seismically active region. When the health examination group visited the U.S. in June, however, understanding of the situation surrounding the nuclear crisis was less clear than it is now. Comparing the three occasions of my participation in the North America program, I felt the magnitude of my responsibility most acutely this time, since only RERF was responsible for, as specialists, explaining from a scientific perspective radiation's human health effects. Dr. Makoto Matsumura, who reported on his visit to the devastated Fukushima area to provide support, also indicated that RERF's continued role in the North America program as an expert organization in A-bomb radiation research was strongly anticipated. I was reminded then that RERF is involved in the program as the sole comprehensive radiation specialist organization, and that in addition to conducting collaborative studies at RERF, it will be important for us, without resting on our laurels, to prepare ourselves to be able to explain an extensive range of issues related to radiation effects in emergency situations such as the much talked about Fukushima nuclear crisis.

The U.S. and Japanese staff involved in the A-bomb survivors' health examination program in Los Angeles. Dr. Akihiko Suyama is the second person from right in the first row.

In Memoriam: Mrs. Ruth W. Beebe

We were saddened to learn that Ruth W. Beebe died on November 19, 2011, 16 days before her 99th birthday. Born on December 5, 1912, Ruth is well known to the RERF community as she was the widow of Gilbert Beebe, one of the most influential figures in terms of the early days of the Atomic Bomb Casualty Commission (ABCC) and the establishment and implementation of the cohort studies which are the hallmark of today's RERF epidemiological research. Ruth was a graduate of Smith College and met her husband Gilbert when they both had summer jobs at Rockaway Beach, New York. They were married in 1933 and remained married until his death in 2003.

Ruth was trained as a clinical psychologist and received an MA in psychology from Columbia University in 1936. She did doctoral work in psychology at Columbia University Teachers College. In 1943, she took a job at the Child Study Center of Maryland in Baltimore to be near her husband Gilbert who was an Army Captain in the Surgeon General's Office in Washington, DC, soon to become involved in the ABCC. From 1944 when she moved to Washington after the birth of her first child, until 1984 when she retired from Montgomery County Public Schools, Ruth worked full-time as a clinical psychologist and as a child and school psychologist in the Washington area. Having lost her own mother at age 7, Ruth was a loving and devoted mother to her four children. In her retirement she was a volunteer in a number of public service activities. For example, in 1969 and 1970 she participated in and was a leader of more than a dozen workshops on black-white relations and racism. Since 1985, she was a member of the Washington-Tokyo Women's Club.

In 1958, she traveled to Japan with her four children to live for two years while her husband served as Chief of Statistics at ABCC in Hiroshima and Nagasaki, Japan. They were to return for two-year assignments in 1966 and 1973 where Gilbert established and secured his reputation and legacy as a devote supporter of ABCC and RERF research. But Ruth was also very busy in Hiroshima. She worked as a school psychologist for the Department of Defense Dependent Schools in Japan and psychological consultant at the American School in Japan, ASIJ. In addition, she gave courses in the University of Maryland Overseas Program's Far East Division, and at Hiroshima University. She was an instructor for the Mazda Motor Corporation and a consultant for the Hiroshima International School which is celebrating its 50th anniversary this year.

After her husband's death in 2003, Ruth began a long descent into dementia while maintaining good physical health. According to her son Alfred, she died peacefully in her home in the company of her youngest son, his daughter, and her caregiver, Marie Davids. She is survived by a daughter Beatrice and three sons, Alfred, Brian, and Christopher, and by five grandchildren and two great grandchildren. The family has asked for donations in honor of Ruth White Beebe to be made to the Alzheimer's Association (www.alz.org) or to the Alzheimer's Foundation of America (www.alzfdn.org). The family should rest assured that many readers of this *RERF Update* will have many fond memories of their mother.

Ruth W. Beebe (center) with her husband Gilbert (right) and son Alfred (left) at the First Annual Gilbert W. Beebe Symposium held at the National Academies in Washington, DC, 2002.

A Surge in RERF Website Accesses

In response to the Fukushima Dai-ichi nuclear power plant accident on March 11, RERF notified the general public on March 15, on its website's "What's New" page, of the availability of brochures describing radiation and its effects on human health. On March 17, a special webpage devoted to the nuclear power crisis was created to provide additional information. The new webpage included a collection of questions and answers regarding radiation health effects, some relevant brochures, a listing of institutes related to health care for the radiation-exposed in Japan, and other related information from both Japan and abroad. An English version of the webpage was made available on March 18, and thereafter, the webpage has been updated when necessary.

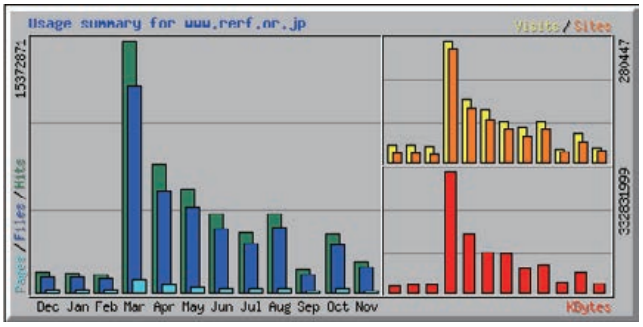
During the same time period, RERF website accesses dramatically increased. The number of daily hits (including hits by a search engine) and visits (actual visits to the RERF homepage) increased from about 40,000 and 1,300, respectively, before the disaster to about 2 million and 30,000, respectively, afterwards (as of March 15). Thereafter, the numbers gradually decreased but remained about five times as many as the pre-accident numbers over a period of several months. Around September, six months after the accident, the access numbers returned to nearly pre-accident levels. The table below shows the numbers regarding RERF website access from February 2011 (before the accident) through October 2011.

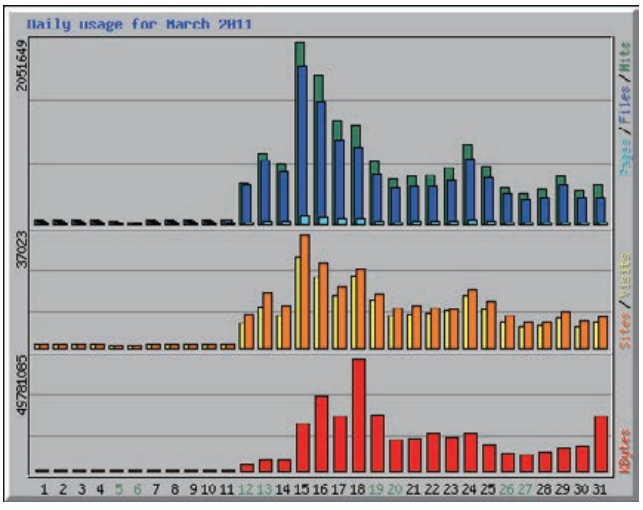
Furthermore, the "Research Questions" page on the external website has received a large number of questions from both inside and outside Japan during the period from the immediate aftermath of the accident to the present. In addition, about 20 organizations, including municipal governments, public research institutes, and libraries, have requested a link to the RERF website. Visitors to the Hiroshima Laboratory also have drastically increased: that number from both inside and outside Japan during the period from January through November 2011 reached 1,640 people, excluding the 1,375 visitors to the Open House event. We have also received requests for radiation-related lectures from various groups and individuals, including community centers, schools, businesses, and physicians, and in response, RERF officers and research scientists provided lectures at 14 venues, including Sendai, Nagoya, and Okinawa, from April until the end of this November. Reservations have been made for dispatching RERF lecturers through February 2012.

In summary, Japan and the world have turned to the contributions and participation of the A-bomb survivors, and the results of the studies and analyses of RERF scientists, for a better understanding of the potential health risks associated with the events happening in northern Japan. We will continue to try our best to make the results of our research known as we apply for a public-interest incorporated foundation status.

Access to the RERF Website
(February–October 2011)

	No. of Hits	No. of Visitors
February	1,119,216	37,174
March	15,372,871	280,447
April	7,858,477	145,136
May	6,297,095	121,818
June	4,842,019	93,466
July	3,710,524	81,469
August	4,830,586	94,307
September	1,422,851	31,124
October	3,623,405	65,854





Research Protocols Approved in May–October 2011

RP 4-11 Genetic Study of Atomic-bomb Radiation by Using HD-microarray CGH Analysis
Kodaira M, Satoh Y, Furukawa K, Nakamura N, Asakawa J

The genetic effects of atomic-bomb (A-bomb) radiation (trans-generational effect) have not been fully elucidated due to low rates of both spontaneous mutation and radiation-induced mutation in germ cells. Since radiation-induced mutations are primarily deletions initiated with DNA double-strand breaks, we propose a comparative genome hybridization (CGH) study using high-density microarrays. In the proposed study, we will analyze a total of 688 DNA samples from both parents of 184 families (high-dose exposure is limited to either parent) and 320 offspring (160 from paternally and 160 from maternally exposed families). We plan to use a 3 × 1.4 M high-density microarray that contains three identical sets of 1.4 million probes (average interval 2.2 kb) on a single slide. The multiplex format of the microarray permits us to analyze three DNA samples at a time on a single slide. We will determine the parental origin of mutations to be detected based on the single nucleotide polymorphism (SNP) information existing in the genome region involved in the mutational events. The analyses of 320 offspring will enable us to test 7.36×10^6 loci that were exposed and unexposed, respectively, assuming that our genome consists of 23,000 genes. If we use the currently available mutation rates obtained through irradiation of spermatogonia of male mice, we would expect 16.2 mutations (95% confidence interval [CI]: 9–25) among the exposed paternal alleles and 3.7 mutations (95% CI: 0–8) among the unexposed alleles (the estimated statistical power to detect radiation effect is more than 80%). On the other hand, we do not expect enough mutations in 160 offspring of the maternally exposed families to detect an elevated rate because the mutation rate obtained in irradiated rat immature oocytes seems to be much lower than that in mouse spermatogonia. Nonetheless, this group is indispensable because the paternal alleles are not exposed to radiation and hence serve as the control of the above-mentioned paternally exposed families. The analyses will provide far more information than is currently available on the risk associated with either maternal or paternal radiation exposure.

RP 5-11 Extension of Study Period (to 2005) and Amendment of Review Procedures of the "Studies on Thyroid Tumor Incidence among the RERF Extended Life Span Study Cohort, 1950–87" (Addendum to RP 6-91)
Ozasa K, Yonehara S, Ito M, Tokuoka S, Sekine I, Suyama A, Furukawa K, Mabuchi K

A site-specific cancer study for the thyroid gland has been underway for the period of 1950–95 (the period was originally defined as 1950–87, then extended to 1995). However, the period of 1950–95 seems to be outdated and needs to be extended again. We also propose to amend the methods for the pathological review to shorten the study period. This is based on the findings in the study for 1950–95 that the reviewers' diagnoses for thyroid tumors were mostly consistent with the registry's diagnoses in recent years. This memorandum describes an extension of the study period and amendment of the pathological review procedures in the RP 6-91.

RP 6-11 A Study of Chromosome Aberration Frequency in Thyroid Cells Following Fetal Exposure to Ionizing Radiation in Mice
Hamasaki K, Noda A, Nakamura N, Hsu WL, Kodama Y

Through epidemiologic studies on childhood cancer conducted since the 1950s, it has been suggested that fetuses are highly sensitive to radiation for induction of cancers. However, whether the third-trimester exposure to diagnostic X rays has induced childhood cancers or not is still under debate. At RERF, we found that peripheral blood lymphocytes of A-bomb survivors who were exposed *in utero* did not record chromosome damage when examined at the age of about 40 years, while the lymphocytes of the mothers showed a clear dose-related increase of translocation frequencies. A similar lack of response was obtained in mouse lympho-hematopoietic cells (peripheral blood T cells, spleen T cells, and bone marrow cells) following fetal irradiation and examination in adult mice. However, our latest results in rat mammary epithelial cells showed that the radiation effect (chromosome aberrations) was clearly maintained in adult rats that were irradiated as fetuses, and the frequency was nearly the same as that of the irradiated mothers. Therefore, it is suggested that chromosome aberration frequency in adults following fetal irradiation may vary among tissues. In the present study, we propose to examine thyroid epithelial cells in mice to see whether or not the radiation effect may be recorded like mammary epithelial cells following fetal irradiation. The thyroid cells were chosen since the thyroid gland is known to be one of the organs more susceptible to radiation-induced carcinogenesis as is the mammary gland. The results may help to explain the cancer risks of A-bomb survivors who were exposed *in utero*.

RP 7-11 Preservation of Fresh Thyroid Samples Obtained from Adult Health Study Participants (Addendum to RP 2-86)

Imaizumi M, Ohishi W, Sera N, Hida A, Yamada M, Hamatani K, Suyama A, Ozasa K, Fujiwara S, Akahoshi M

Thyroid cancer is one of the cancers most affected by radiation and shows increased incidence with increase of radiation dose among A-bomb survivors. In recent years, genetic studies of thyroid cancer have achieved significant progress mainly in terms of *RET/PTC* rearrangements and *BRAF* mutations. However, it is not the case that mechanisms behind thyroid cancer development and radiation effects on such mechanisms are fully understood. For elucidation of molecular mechanisms of thyroid cancer development among A-bomb survivors, collection and storage of thyroid tumor samples are indispensable. With introduction of thyroid ultrasound screening to health examinations conducted by RERF's Departments of Clinical Studies (Hiroshima and Nagasaki), a large number of thyroid tumors are now being detected. It is believed that future collection of as many thyroid tumor samples as possible, without regard to radiation dose or distinction between benign and malignant tumors, would contribute to mechanistic elucidation of thyroid cancer development and radiation carcinogenesis.

In accordance with research protocol (RP) 2-86 "Collection of surgically removed cancer tissues from A-bomb survivors: Special reference to thyroid and breast cancers," RERF has worked on collection and cryopreservation of fresh thyroid cancer tissues from A-bomb survivors and nonexposed controls, with an eye on their use for future molecular biological studies. The present RP, an addendum to the aforementioned RP 2-86, aims at preservation of fresh thyroid tumor tissues surgically removed from the Adult Health Study subjects for future studies including gene analyses.

Recent Publications

(Japanese): the original article is in Japanese.

Abe H, Ochi H, Maekawa T, Hayes CN, Tsuge M, Miki D, Mitsui F, Hiraga N, Imamura M, Takahashi S, Ohishi W, Arihiro K, Kubo M, Nakamura Y, Chayama K: Common variation of IL28 affects gamma-GTP levels and inflammation of the liver in chronically infected hepatitis C virus patients. Journal of Hepatology 2010 (September); 53(3):439-43.

Fujiwara S: Importance of raising awareness about spontaneous insufficiency fractures in the bedridden elderly. International Journal of Clinical Rheumatology 2010 (August); 5(4):395-7.

Fujiwara S, Hamaya E, Goto W, Masunari N, Furukawa K, Fukunaga M, Nakamura T, Miyauchi A, Chen P: Vertebral fracture status and the World Health Organization risk factors for predicting osteoporotic fracture risk in Japan. Bone 2011 (June); 49(3):520-5. (RERF Report 4-10)

Grant EJ, Neriishi K, Cologne JB, Eguchi H, Hayashi T, Geyer SM, Izumi S, Nishi N, Land CE, Stevens RG, Sharp GB, Nakachi K: Associations of ionizing radiation and breast cancer-related serum hormone and growth factor levels in cancer-free female A-bomb survivors. Radiation Research 2011 (June); 176(5):678-87. (RERF Report 6-10)

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