放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
Volume 22, Issue 1, 2011

Radiation Effects Research Foundation

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This newsletter is published by the Radiation Effects Research Foundation (formerly the Atomic Bomb Casualty Commission), established in April 1975 as a private, nonprofit Japanese foundation. It is supported by the government of Japan through its Ministry of Health, Labour and Welfare and that of the United States through the National Academy of Sciences under contract with the Department of Energy.

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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From the Editors

Welcome back!

The year 2011 was looking a lot like any other year, perhaps with a little longer and colder than normal winter. The rice was pounded into mochi by RERF employees at the New Year Party, and the annual meeting of the Scientific Council was concluded after much preparation by RERF's research staff. But on March 11, one of the world's largest earthquakes generated an unusually large tsunami and RERF's typical scheduled activities were about to change. One of us [EBD] will never forget walking down the stairs into the clinical studies reception area and seeing RERF's chairman watching the breaking news live on a large television screen; Dr. Okubo turned to me and said "There has been a large tsunami in Tohoku, the northern-most part of Japan's island of Honshu—and it is not good." In the days that followed, the news turned to focus on the effects of the Fukushima Dai-ichi nuclear power plants. The world turned its attention to the country that had previously suffered exposure to radiation and to the institution whose studies of the A-bomb survivors have contributed major information for mankind's risk estimates about radiation health effects. Ironically, on March 14, the American Medical Association's *Journal of Disaster Medicine and Public Health Preparedness* would publish a special supplement titled "Nuclear Preparedness" that would include a cover-story article reviewing the work and findings of the ABCC and RERF. In this issue of *Update*, please read Chairman Okubo's message about RERF's role in the continuing disaster and personal accounts of RERF employees who were sent to assist the survivors in Tohoku.

Cherry blossoms in full bloom and "RERF" letters in phlox flowers

In addition to other news regarding RERF, you will also find in this issue a report on the 38th Scientific Council meeting, an update on RERF's transition to a public-interest incorporated foundation, reports of two workshops held at RERF, and two articles describing the research activities of the departments of Epidemiology and Statistics. Finally, two human interest notes are included by two long-term supporters of ABCC and RERF, William "Jack" Schull and Kazuo Neriishi.

The cherry blossoms (sakura) and other signs of spring would eventually emerge, but Ohanami Parties were much less frequent and more subdued as thoughts continually turned to those most afflicted in the north as efforts continue to attempt to resolve the power plant conditions. Meanwhile, thanks to RERF's Midori no Kai (Green Thumb Club), employees were cheered up daily by a beautiful planting that spelled out "RERF." We hope that you will 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

Special Message from Chairman Toshiteru Okubo

We would like to offer our deepest condolences to all those affected by the recent earthquake that struck in Japan's Tohoku region. In response to the accident at the Fukushima Dai-ichi nuclear power plant, RERF has enhanced our activities with other related organizations for support of medical countermeasure efforts, including the dispatch of radiation specialists to the affected region. (See articles

on the activities reports in Fukushima and Yamagata on pages 6–8.)

It is hoped that the radiation-related information posted on our website can help resolve any questions and concerns about radiation. We also fervently hope and pray for the affected region's timely recovery.

We have thus far screened 30 individuals coming from Fukushima Prefecture for radioactive contamination, but no one needed decontamination. Since it is expected that there will be more such requests, we will coordinate such efforts with Hiroshima University and the Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, as the designated dosimetry organizations in Hiroshima Prefecture. In addition, we are participating in a Chromosome Network, and will assist with the dosimetry of workers at the nuclear plant by analyzing chromosome images sent by the National Institute of Radiological Sciences.

RERF's website has been expanded to provide additional radiation-related information to the general public. The traffic to the site has soared since the nuclear accident, and the number of visitors on a peak day was equivalent to that of four months normal traffic. Even today, daily traffic to the site continues to be that of a former two months. We received numerous telephone inquiries in the week following the accident, particularly from the members of the media, but the number of calls has now decreased. The Public Relations and Publications Office is responding to such inquiries utilizing the technical expertise of RERF's research scientists.

Members of the Hiroshima Prefectural Police, after their return from providing assistance in Fukushima Prefecture, undergo screening for contamination at RERF (see also cover photo).

RERF is able to contribute to the design and implementation of long-term epidemiological follow-up research, and is preparing to respond to such requests promptly.

Report on the 38th Scientific Council Meeting, 2011

The 38th Scientific Council (SC) met from February 28 to March 2, 2011 in Hiroshima, Japan to review RERF's scientific programs. It was co-chaired by Dr. Kiyoshi Miyagawa and Dr. David Hoel. Dr. Kazuo Tajima, Director of the Aichi Cancer Center Research Institute, joined the SC with the expiration of the term of Dr. Yoshiharu Yonekura. Four additional experts were invited to be special councilors to assist the SC in an in-depth review of the Departments of Epidemiology and Statistics. They were Dr. Suminori Kono of Kyushu University, Dr. T. Shun Sato of Kyoto University, Dr. John Boice of Vanderbilt University, and Dr. Colin Begg of Memorial Sloan-Kettering Cancer Center.

RERF Chairman Dr. Toshiteru Okubo welcomed the SC members and guests and expressed how important the SC's work is to the staff of the RERF. He also briefly explained some changes that will come about as RERF becomes a public-interest incorporated foundation. The Scientific Councilors will become the Scientific Advisors (Scientific Advisory Committee) who will continue to review the scientific programs of RERF.

Responses to last year's SC general recommendations and highlights of research accomplishments during 2010 were summarized by Dr. Roy Shore. In response to the 2010 SC recommendations, we have made progress in integrating and focusing on RERF project priorities. Departments have held meetings or mini-retreats to define study priorities and achievement milestones. Experience has shown that both broad, thematic working groups and smaller, more focused "mini-working groups" are beneficial, so both are being used strategically. Regarding a centralized database that integrates all available information and biosamples on study participants, a key issue is having a user-friendly database system that is fully cross-indexed and documented and can be accessed in a variety of ways. RERF committees on data and biosample management are currently working on various aspects of this. Regarding increased statistical bioinformatics support, the Statistics Department has been conducting bioinformatics seminars and is working with the basic science departments on

studies that have large arrays of genetic or phenotypic measurements. Regarding increased first-authored publications and mentoring of young scientists, departmental leaders have been asked to monitor progress on publications and to develop plans for mentoring.

Accomplishments during 2010 include the initiation of the F_1 longitudinal clinical examination program for nearly 12,000 F_1 participants, and the completion of the initiative that added 1,900 new screenees under the age of 10 years at the time of the A-bomb to the Adult Health Study (AHS) in order to strengthen the study's precision in estimating risks after childhood exposure. An international workshop was held on the epigenetic effects of radiation, which stimulated internal research on epigenetic radiation effects. Significant progress has been made in updating the tumor registries and the dosimetry databases. Major publications this past year pertained to radiation risk for heart disease, myelodysplastic syndrome, cataracts, and second primary cancers, the development of a tooth-enamel-based neutron biodosimeter, and the joint effects of radiation and smoking on lung cancer risk.

Several important new projects were initiated during 2010. To follow-up on the early ABCC findings regarding cognitive deficits among those with *in utero* radiation exposure, a study was initiated on late-life neurocognitive function among AHS participants exposed *in utero* or in early childhood. To learn more about the mechanisms by which radiation exposure may increase the risk of circulatory diseases, new AHS studies have been implemented on physiological indices of arteriosclerosis and on measurements of circulatory disease-related cytokines. To experimentally verify radiation-related circulatory disease effects at moderate doses, a study of the incidence of hypertension and stroke is being undertaken over the dose range of 0–4 Gy in a strain of rats susceptible to the two endpoints.

A summary review of scientific transparency and data sharing at RERF was given. Over 10 major RERF datasets are publicly available on our external website. They have been widely accessed as researchers from 41 different countries have made about 470 data downloads in the past three years. Furthermore, during 2010 more than 60 studies with external collaborators were ongoing that involved individual data or biospecimen sharing.

The general recommendations this year by the SC included the following:

- Clear articulation of the justification, prioritization, and overall quality of each research project is needed. Research proposals (RPs) need to address topics of compelling relevance to current scientific knowledge and better articulate the scientific rationale. A clear written framework for RPs would be helpful, as well as assigning priority scores to RPs.
- Contemporary scientific advances increasingly require inter-disciplinary collaborations and separate programmatic structures to facilitate them. The program themes should be selected on the basis of the overarching research priorities of RERF, and these could be periodically updated to reflect the contemporary landscape of research emphasis.
- The many and varied databases of participant information and biological samples should be integrated into a central database for the use of researchers in all departments. The database would also require user-friendly database software that researchers could use to retrieve the data.
- Biological samples are a very important scientific asset of RERF. Since current biosample storage space will soon be filled, RERF must give the highest priority to finding space for these unique biological samples.
- With the limited availability of government research funds it is important to facilitate applications for extramural funding. It is also important that travel funds for international scientific meetings be protected, so that RERF scientists can present their seminal findings to the world as well as stay current on the latest research relevant to radiation health effects.
- Collaborations with universities and other Japanese colleagues should be strengthened, and more graduate students and postdoctoral fellows should be recruited to engage in research based on RERF's unique resources and databases.
- High quality publications are essential for informing the world of new findings and for the continued success of RERF. More such publications are needed.

Highlights of some of the main recommendations for individual departments or offices are:

- Pilot studies should incorporate clear milestones for making decisions on when the results of the pilot study indicate a high probability of success for a larger scale study versus when a study should not be pursued further.
- As much as possible, a full range of confounding factors should be considered in interpreting study results.
- An updating of the denominators for the Life Span Study (LSS) cancer incidence studies will be of much value.
- Comparing disease rates in RERF epidemio-

logic cohorts with general population rates can be useful. Such population comparisons add an additional perspective, especially when evaluating rare outcomes such as mesothelioma.
- Collaborative work should enjoy high priority in the overall mission of the Department of Statistics. The reviewers are pleased that the department takes a proactive approach to consulting, beginning with early involvement in study design.
- Original research on statistical methodology should continue to be an important goal of the Statistics Department. This will encourage the professional staff to maintain an interest in developments in the field, generally enliven the intellectual environment, and ideally bring recognition to the department.
- The F_1 offspring are still young and further follow-up is highly recommended. It should be noted that this type of study has not been undertaken anywhere else in the world.
- The F_1 clinical examination program should consider a systematic examination of F_1 study subjects for congenital defects.
- Investigation of the biological significance of *ALK* rearrangements newly found in papillary thyroid cancer is needed to clearly support their role in carcinogenesis. Establishment of mammalian cells or transgenic mice harboring the rearranged *ALK* gene should be a high priority.
- The pilot influenza vaccination study should incorporate a careful evaluation of previous infections and the previous vaccination history of each subject.
- More comprehensive genomic approaches, such as multiplex single nucleotide polymorphism (SNP) typing for multiple candidate genes, genome-wide SNP typing, and genome-wide array-based methylation assays should be considered and encouraged where appropriate.
- Even in its transition years, the Genetics Department should act as the genetic counselor to the entire enterprise, bringing awareness and access to all the astonishing advances in genetics and genomics as applied to the mission of RERF.
- As the first test of the methodology of next-generation DNA sequencing, the sequencing of chromosome 19 is planned for some study subjects. A long-term strategy for future massive sequencing of a large number of family samples should also be considered.
- The analysis of copy number variants using high-density microarrays in mouse strains has provided a sound basis for this technology in the Genetics Department. The technology is now ready for extending to the study of the genetic effects of atomic-bomb radiation.
- Sample collection and storage activities should be consolidated in a specialized support section, rather than being the responsibility of individual research sections.
- Emphasis should be given to producing well-written press releases at the time of major RERF publications.

In summary, the SC highlighted the unique role of RERF in informing the world about radiation effects, and they called for additional attention to research priorities, inter-disciplinary and collaborative research, integrated databases, and publication productivity.

RERF Scientific Councilors

Dr. David G. Hoel, Co-chairperson, Distinguished University Professor, Department of Medicine, Medical University of South Carolina

Dr. Kiyoshi Miyagawa, Co-chairperson, Professor,

Participants of the 38th Scientific Council meeting (Hiroshima Laboratory)

Laboratory of Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo

Dr. Takashi Yanagawa, Professor, The Biostatistics Center, Kurume University

Dr. Katsushi Tokunaga, Professor, Department of Human Genetics, Division of International Health, Graduate School of Medicine, The University of Tokyo

Dr. Kazuo Sakai, Director, Research Center for Radiation Protection, National Institute of Radiological Sciences

Dr. Kazuo Tajima, Director, Aichi Cancer Center Research Institute

Dr. Marianne Berwick, Professor and Chief, Division of Epidemiology and Biostatistics and Associate Director, Cancer Research and Treatment Center, University of New Mexico

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

Dr. Michael N. Cornforth, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch

Dr. Sally A. Amundson, Associate Professor of Radiation Oncology, College of Physicians and Surgeons of Columbia University

Special Scientific Councilors

Dr. John D. Boice, Jr., Professor of Medicine, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center

Dr. Colin Begg, Chairman, Department of Epidemiology and Biostatistics, Eugene W. Kettering Chair, Memorial Sloan-Kettering Cancer Center

Dr. Suminori Kono, Professor, Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences

Dr. T. Shun Sato, Professor, Department of Biostatistics, Kyoto University School of Public Health

Hiroshima Governor Hidehiko Yuzaki Visits RERF

In the morning of January 19, Hiroshima Governor Hidehiko Yuzaki, who assumed his office in November 2009, visited the Hiroshima Laboratory. He received briefings at the Chairman's office from Dr. Kazunori Kodama, Chief Scientist, on RERF's research and then from Dr. Toshiteru Okubo, Chairman, on RERF's current status and future plans. Afterwards, Governor Yuzaki spoke with the directors and senior staff, and toured the RERF facilities led by Dr. Okubo and Mr. Eiji Akimoto, Chief of Secretariat.

After the Fukushima Dai-ichi nuclear power plant accident, Governor Yuzaki emphasized the importance of utilizing the knowledge and experience accumulated in Hiroshima and Nagasaki for over 60 years. He announced that utmost cooperation will be extended to the long-term health management of Fukushima residents in the future, including training for doctors, nurses, and radiological technicians, through the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE), consisting of Hiroshima Prefecture, Hiroshima City, RERF, and other A-bomb-related organizations in Hiroshima.

Hiroshima Governor Hidehiko Yuzaki (left) touring RERF with guidance from Chairman Toshiteru Okubo (far right)

Dispatch of RERF Staff to the Area Affected by the Fukushima Dai-ichi Nuclear Power Plant Accident

In response to the accident at the Fukushima Dai-ichi nuclear power plant, RERF received two requests regarding the dispatch of radiation specialists in March 2011. At the request of the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE), Mr. Toshinori Kurisu (radiological technician, Department of Clinical Studies, Hiroshima) was dispatched to Fukushima Prefecture as a member of its radiation measurement team. The other request came from the Yamagata Prefectural Office via the Ministry of Health, Labour and Welfare (MHLW), and Dr. Norio Takahashi (research scientist, Department of Genetics) and Mr. Katsuhisa Yamasaki (radiological technician, Department of Clinical Studies, Nagasaki) were dispatched to the prefecture to engage in radiation measurements and provide health consultation. All three completed their duties successfully and returned safely after one week. We have asked them to write about their experiences in the affected area.

Report on Dispatch to Fukuyama Prefecture in Response to Tohoku Earthquake

Toshinori Kurisu, Assistant Chief of Technicians
Department of Clinical Studies, Hiroshima

On March 15, the Fukushima prefectural governor (via the Fukushima Prefectural Disaster Countermeasures Office) made an urgent request to Hiroshima's governor for dispatch of radiological technicians and nurses, to deal with the situation at the Fukushima Dai-ichi nuclear power plant damaged by the earthquake that struck off the coast of eastern Japan on March 11. In response, the Hiroshima prefectural government requested the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) to organize and dispatch a radiation dose-measurement team, and I was dispatched to Fukushima prefecture from March 16 to 22, 2011, as a sub-leader of the team of six members.

In collaboration with the Fukushima Central Prefectural Public Health Center (Sukagawa City), we visited the shelters in the center's jurisdiction, and conducted screening tests and decontamination if any contamination was found. We also issued screening measurement certificates indicating the test results. None of the measurement values reached the level requiring decontamination designated by the Fukushima government. We examined a total of 1,447 persons at 12 shelters in five cities and towns.

For those showing a higher than background level but not high enough to require decontamination, we first explained while showing them their measurement results that their clothes such as coats and socks contained small amounts of radioactive substances. Even though most of the affected people evacuated their homes without any extra clothes and could not take a bath or a shower in the shelters, we explained that, as soon as the inconvenience that they were experiencing improved, it was desirable to take the following measures: 1) take a bath/shower, 2) change clothes, 3) wash the clothing containing radioactive substances as would be done normally, 4) wipe with a slightly damp towel the items that cannot be washed, 5) place such items into plastic bags, shut the bags tightly and store them in a separate area, if they cannot be washed right away, in order to prevent vaporization of iodine and scattering of radioactive dust, and 6) wash shoes with water and wipe any mud off the soles. Among those measures, we were able to confirm later that bathing and laundering were effective because we found that there was a clear difference between the values before and after such measures were taken.

In conducting effective and efficient screening of radiation contamination for a large number of residents without sufficient equipment and manpower, there is a risk of delayed decontamination treatment due to long waiting times and of secondary contamination via those already contaminated. In order to avoid such a situation, it is necessary to

Radioactive contamination screening for Fukushima residents at Miharu Junior High School, one of the evacuation sites (Toshinori Kurisu, second from right)

identify those potentially contaminated as soon as possible and to decontaminate them promptly to prevent secondary contamination. One solution is to use environmental measurement equipment to measure only the shoe soles of residents instead of scrutinizing the entire body from the beginning, triaging those at a certain radiation level for priority screening. By doing so, health hazards can be reduced and prevented and the spread of contamination avoided.

I would like to express my heartfelt sympathy to all those affected by the disaster and offer my deepest condolences to the victims. I truly hope that restoration of the affected areas is achieved at the earliest possible date.

Dispatched to Help People Evacuated from Fukushima Prefecture to Yamagata Prefecture

Norio Takahashi, Research Scientist, Department of Genetics
Katsuhisa Yamasaki, Senior Technician, Department of Clinical Studies, Nagasaki

We were dispatched to Yamagata Prefecture for eight days from March 17 through 24, 2011, at the request of the prefectural government through the Ministry of Health, Labour and Welfare. We were told that our mission would be to measure radiation contamination levels of people from Fukushima Prefecture who had been forced by the nuclear power plant emergency to take refuge in Yamagata Prefecture. Many people were evacuated from the government-designated evacuation zone. About 1,000 took shelter in the city of Yonezawa. Before we left Hiroshima, we had seen film footage of some officials busily measuring contamination levels in the evacuees.

A blizzard warning had been issued in the weather forecast for the city of Yamagata for March 17. We were thus skeptical as to whether or not we could arrive at our destination. Regardless, we left for Yamagata. When departing RERF, we received words of encouragement and advice from Chairman Toshiteru Okubo and many others, with an emergency food supply and plastic bottles of water—a package hastily arranged by the General Affairs Section and enough for us to survive a week—in hand. That was the beginning of our "eight extraordinary days."

Our plane managed to land at Yamagata Airport, which was buried in more snow than I have ever seen in Hiroshima, after dodging many potential problems on the way. There, we were greeted by Mr. Hiroyuki Satoh of the Department of Health and Welfare, Yamagata prefectural government, our host. When we arrived at the Yamagata prefectural government office, we were surprised to hear that the governor was expecting us. During our talk with the governor and the chief of the Health and Welfare Department, among others, we came to understand that our mission was not limited to measurement of contamination levels but was actually four-fold: 1) to give advice to those concerned in the local community on establishment of systems for detecting levels of radioactive surface contamination and removing such radioactive particles; 2) to give lectures on radiation to the staffs of the prefectural government and local public health centers; 3) to inform people who took shelter in Yamagata Prefecture of the radiation doses people might be exposed to in the prefecture and other relevant information in order to relieve undue anxiety; and 4) to provide a feeling of security to the residents of the prefecture through the mass media. We began our activities in line with the mission.

The evacuees, excluding those who voluntarily took shelter at private facilities (e.g., hotels), were staying in groups at about 50 public facilities (e.g., gymnasiums). Some facilities, such as the Yamagata municipal gymnasium, accommodated more than 1,000 evacuees, while others housed just a handful. All the evacuees were taken care of by public health nurses affiliated with four local health centers, each of which is located in one of the four administrative districts that the prefecture of Yamagata is divided into for governance. There is one branch health center in the city of Yamagata.

Therefore, as a first step, we formulated instruction manuals for 1) establishment of definitions of contamination and non-contamination, 2) identification of individuals requiring surface contamination tests, 3) surface contamination tests and use of testing equipment, and 4) removal of radioactive particles from clothing and the like as well as from body surfaces, and management and storage of contaminated clothes and items used for such removal. The work was carried out in consultation with the chiefs of the health centers and representatives of various hospitals in the cities of Yamagata and Yonezawa, which had received large numbers of evacuees.

As a second step, we gave a lecture to the prefectural government staff, and also visited the health centers to brief public health nurses on the above instructions and radiation. Each of the lectures was attended by 30 to 50 individuals, who listened with intense interest. Questions those individuals had been asked by evacuees were shared and possible responses were discussed as case studies.

We went on to visit six facilities housing evacuees to explain to them that the free-in-air (FIA)

radiation doses in Yamagata Prefecture posed no danger to human health. Some evacuees said that the information regarding the area of their original home was more important than information about Yamagata Prefecture, and therefore when we were interviewed by the broadcast media later, we proposed to the stations that they air information concerning Fukushima Prefecture, as it was important to the evacuees.

We received media coverage at the governor's press conference. We said that there was no difference between FIA doses in Yamagata Prefecture and normal values measured nationwide and that, although there was no need to be overly concerned, residents must keep an eye on possible changes in the future and take appropriate action. (A video of the interview was made available on the prefectural government's website.) The governor later said to us that the press conference reassured residents of the prefecture and helped them handle the situation calmly, making us feel that our visit to Yamagata was of some help. We were interviewed by reporters on many other occasions. And at such times, we did our best to describe the situation in the prefecture as plainly and as clearly as possible.

Toward the end of our stay, radioactive contamination of spinach and milk was reported. The staff of the prefectural Department of Agriculture, Forestry and Fisheries asked us about effects of radioactive fallout on agricultural products. As we had no relevant information, we provided information that we obtained from the National Institute for Environmental Sciences and other organizations after arriving back in Hiroshima. We were told that the staff of the department were appreciative of the information.

Norio Takahashi (second from left) and Katsuhisa Yamasaki (second from right) briefing Yamagata Governor Mieko Yoshimura (center)

In concluding our report, we would like to pay our respects to the governor of Yamagata Prefecture, Mieko Yoshimura, and the staff of the prefectural government. We also want to note that we were deeply impressed by the self-sacrifice and dedication of Mr. Satoh and Mr. Masahide Sudoh, chief of the Public Health and Pharmaceutical Affairs Section of the prefectural Department of Health and Welfare, as well as of the public health nurses at the local health centers. Hang on, Yamagata! Keep your chin up, Tohoku!

Transition to Exceptional Incorporated Foundation with Councilors

As the preliminary stage for its transition to a public-interest incorporated foundation, RERF obtained approval for changes to its Act of Endowment on April 1, 2011, and on April 4 the foundation transitioned to an exceptional foundation with Councilors by registering as such. The new moniker, however, is strictly for legal purposes, with the foundation continuing to be referred to by its conventional name of the Radiation Effects Research Foundation.

As an exceptional foundation with Councilors, RERF is now equipped with a Board of Councilors, which serves as the foundation's decision-making body and consists of eight newly appointed Councilors. Without any change in name, the Board of Directors will serve as RERF's executive committee, with its three previous Permanent Directors appointed as Directors. The number of Auditors, two, remains the same as before.

Aiming at official transition to a public-interest incorporated foundation in April of next year, RERF plans to quickly apply for Cabinet Office approval upon finalizing matters required for the transition at the meetings of the Board of Directors and the Board of Councilors in June of this year.

Officials from Fukushima Medical University Visit RERF

On April 25, six officials of Fukushima Medical University, including Dr. Seiichi Takenoshita, Vice Chairman of the university, visited RERF's Hiroshima Laboratory and were greeted by Dr. Toshiteru Okubo and other directors, the Associate Chief of Research, Chief Scientists, and Chief of Secretariat. Dr. Okubo and Dr. Kazunori Kodama briefed the visitors at the Auditorium on the forward-looking studies of health effects of radiation that have been conducted by ABCC-RERF over the years. The briefing session was followed by a tour of such RERF research departments as the Departments of Clinical Studies, Epidemiology, and Information Technology. The visitors mentioned later that it had been very meaningful to see the actual site where studies are being conducted in the A-bombed city of Hiroshima, as the experience would help them establish a system to provide security and safety for the residents of Fukushima Prefecture for many years to come, with active discussion between the group and RERF representatives continuing even after the facility tour. The next day, April 26, they visited the Nagasaki Laboratory and were briefed by Dr. Masazumi Akahoshi, Chief of the Department of Clinical Studies, on the studies conducted in Nagasaki.

Officials from Fukushima Medical University touring RERF with guidance from Chairman Toshiteru Okubo (left)

Staff News

Kazuo Neriishi, Assistant Chief, Department of Clinical Studies, Hiroshima, retired on December 31, 2010 at the mandatory age and was appointed Consultant of the department as of January 1, 2011; he has shared some of his memories of his research career in Human Interest Notes (see page 30). **Fumiyoshi Kasagi**, who remained as Assistant Chief, Department of Epidemiology, Hiroshima, since July 1, 2009 after his mandatory age retirement, resigned on March 31 and joined the Radiation Effects Association in Tokyo on April 1, 2011.

As we reported in the *Update* last year, **Harry M. Cullings** was promoted to the post of Chief of the Department of Statistics, effective from April 15, 2010. Likewise, **Yoshiaki Kodama** and **Yoichiro Kusunoki** were promoted to Chief of the Department of Genetics and Chief of the Department of Radiobiology/Molecular Epidemiology, respectively, effective from February 1, 2011. With those promotions, every research department now has a chief in place, which is expected to further strengthen the departments and facilitate interdepartmental collaboration. On this occasion, the recently appointed department chiefs were invited to write about their goals in their new positions.

Thoughts on Becoming Chief of Statistics

Harry M. Cullings, Chief
Department of Statistics

I was honored to be asked to take the post of Chief of Statistics after serving in other capacities in the department for about ten years previously. My goals were naturally to guide the Statistics Department in providing the best possible statistical consulting service to other departments, and to have the Department continue the proud tradition of statistical research at ABCC and RERF that has made such a well-known and well-reputed contribution, worldwide, to research on the health effects of ionizing radiation.

As important as methodological developments have been in the past, there are still great challenges remaining for RERF statisticians. RERF has tremendous stores of data that have not nearly been

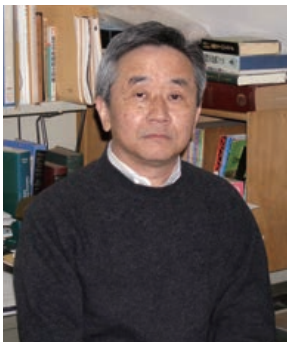
completely explored, but they are fraught with problems such as missing data and measurement error, like most data from observational studies. Technology has been adding greatly to the wealth of data by creating measurements on huge numbers of biological variables that can be obtained from small samples from the human body. As statisticians we need to respond to those challenges by learning new methods and adapting them to the needs of RERF research, and, when possible, participating in their theoretical and practical development.

I believe that the best single thing I can do as chief is to encourage communication and provide a pleasant and supportive work environment that encourages learning and productivity. Group thinking as an input to forming approaches to technical (and other) problems has great value, but it requires that individuals develop trust and confidence in others within the department, which the chief must support and facilitate.

As a statistician, the thing I love most is working on complicated real-world problems and trying to understand what the data are telling me. I feel greatly privileged to be able to continue doing research in areas that interest me in addition to undertaking the responsibilities of being the chief, and to me this is what really makes it worthwhile to work long hours and think about research problems at any hour of the day.

30 Years at Hijiyama

Yoshiaki Kodama, Chief
Department of Genetics

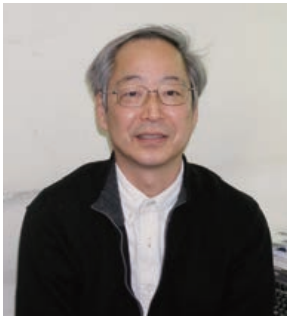


My name is Yoshiaki Kodama, and I recently became Chief of the Department of Genetics. I would like to request your continued support on this occasion. I cannot believe it has been 30 years since I joined RERF. I previously lived in Sado, Mito, and Sapporo before moving to Hiroshima, which marked my first time living in western Japan. I had no idea how hot it would be in Hiroshima and was a little worried about my family before we moved here as we are resistant to cold but sensitive to heat, especially after my mentor had scared me by telling me stories about the blazing temperatures. And he was right! The heat and humidity in the summers of this Seto Inland area was unimaginable for someone like me, coming from an area where your hair often freezes on the way home from a public bath (in winter, of course). However, people really do grow accustomed to new circumstances. Led by our children speaking fluent Hiroshima dialect and not caring at all about the heat, we adapted to life in Hiroshima, although I have to admit I still get excited when it snows. Hiroshima has become the place I have lived the longest in my life.

When I first joined RERF, I found out how strong the organization's mission was for investigating A-bomb radiation effects. Even though it may feel a little uncomfortable to think that everything we do is for the mission, it is quite easy to understand as the raison d'être for the research foundation. The mission of the Department of Genetics is to conduct genetic effects research of A-bomb radiation and biodosimetry studies. Both study areas are time-consuming but important for clarification of late effects of the A-bombings. No genetic effects have been found thus far despite the vast amount of effort we have made. It is expected that a reasonable conclusion regarding this issue will be obtained on the basis of findings from DNA-level research to be conducted in the future. Regardless of the findings we may obtain in the future, this is research that only RERF can carry out, and we should consider it our responsibility to accurately assess effects of A-bomb radiation. Even if we cannot detect genetic effects, we can still learn about an upper-bound limit on risk estimates. I believe we should always keep this in mind as investigators conducting our research mission.

For Mechanistic Research into Radiation's Effects

Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology



I have been recently appointed Chief of the Department of Radiobiology/Molecular Epidemiology (RME) after having served as Acting Chief for the past slightly more than two years. Although I am still inexperienced compared with other senior department chiefs, I am committed to doing my utmost to pursue radiation effects research. I look to all of you for your continued guidance and support.

The linchpin of the research carried out at the RME department is to deepen understanding of

mechanisms behind adverse health effects of radiation. I believe that goal is significant for two reasons. One is that elucidation of such developmental mechanisms of radiation-associated disease could lead to creation of effective methods for prevention and treatment of such disease. The other is that investigation of biomarkers and genotypes related to disease mechanisms allows application of such biomarkers to accurate estimation of disease risk.

Since I joined RERF 25 years ago after leaving graduate school at the Hiroshima University Research Institute for Radiation Biology and Medicine (RIRBM), I have been involved in the conduct of immunological research. Thanks to the cooperation of many A-bomb survivors and RERF staff, I have succeeded in accumulating significant amounts of scientific evidence of changes to the immune system over long periods caused by radiation. Based on such accumulated data, I am hoping to proceed with research on radiation-induced acceleration of immunosenescence and disease risk. Molecular analysis of radiation-associated cancer in our department also requires mechanistic approaches. To develop and expand on this kind of research, valuable findings accumulated from RERF's epidemiological and clinical studies, stored biosamples, and our high-level statistical analysis and information technology capabilities should be fully utilized. In addition, the latest analysis techniques and research methods must be introduced to RERF through collaboration with our Department of Genetics and non-RERF researchers in Japan and abroad. To that end, I would like to ask for your continued cooperation.

To elucidate the mechanisms involved in A-bomb radiation effects, and contribute to efforts toward maintenance of the health of A-bomb survivors. I believe that, for someone born, raised and engaged in research in Hiroshima, this is the best way to inherit the experiences of Hiroshima and Nagasaki and pass that information on to future generations. I look forward to your continued support.

Awards Received by RERF Scientists

Receiving the IAR Prize

Toshiteru Okubo, Chairman

On February 18, 2011, during the 13th meeting of the World Health Organization's (WHO) Radiation Emergency Medical Preparedness and Assistance Network (REMPAN), held at Nagasaki University, I presented a lecture as keynote speaker titled "Long-term epidemiological studies of atomic-bomb survivors in Hiroshima and Nagasaki: Study populations, dosimetry, and summary of health effects," which also had been awarded the 10th International Association of Radiopathology (IAR) Prize. For this honor, I would like to express my heartfelt appreciation to everyone concerned.

Let me explain the background of my lecture presentation. Since this year's REMPAN meeting was held in Nagasaki, a special session concerning A-bomb survivor follow-up studies was scheduled. It was decided at the discretion of Dr. Shunichi Yamashita, Director-General of the aforementioned meeting and professor at Nagasaki University, that RERF would take charge of the relevant session. I opened the session by outlining A-bomb survivor follow-up studies, but it should be mentioned that the IAR Prize was granted not to me as an individual, but to RERF as a whole, and that I received the prize on behalf of RERF as its representative at the meeting. Furthermore, it should be said that the true awardees were instead Drs. Kazunori Kodama, Masazumi Akahoshi, Yoshiaki Kodama, and Hiroaki Katayama, who followed my lecture with their own.

The IAR was established in July 1955 as an international organization by a French physician, the late Dr. H. Jammet, who had served as a member of the U.S. National Council on Radiation Protection and Measurements (NCRP) in the 1950s. The association is composed of researchers around the world in the field of radiology. After the passing of Dr. Jammet, Dr. Shigenobu Nagataki, former RERF Chairman, served as IAR Chair, with Dr. Marc Benderitter from the Institute de Radioprotection et de Sûreté Nucléaire (IRSN) of France recently selected to succeed to the relevant position.


IAR
CERTIFICATE
Professor Toshiteru Okubo
Long-term epidemiological studies of atomic bomb survivors in Hiroshima and Nagasaki: Study populations, dosimetry and summary of health effects

Certificate from the International Association of Radiopathology

It is my fervent hope that RERF will continue to collaborate with such international organizations in the future and

strive to promote fruitful research efforts in the field of radiation health effects.

Receiving a Distinguished Service Award from the Japan Epidemiological Association

Kazunori Kodama, Chief Scientist

At the 21st Annual Scientific Meeting of the Japan Epidemiological Association held on January 21–22, 2011 in Sapporo, I had the honor of receiving a Distinguished Service Award from the Japan Epidemiological Association. Researchers who have made contributions to progress in epidemiology and development of the Association are awarded the Distinguished Service Award by the Japan Epidemiological Association.

I received the award in recognition for my two major contributions; organizing the 17th Annual Scientific Meeting of the Japan Epidemiological Association held on January 26–27, 2007 in Hiroshima and serving as the 6th President of the Japan Epidemiological Association for three years from January 2007 to January 2010.

During my term of office as President of the Association, a decision was made by the government to completely revise the Statistics Act for the first time in 60 years, which raised concerns that use of public statistics by researchers might be restricted, because of the trend toward tighter protection of personal information. The Japan Epidemiological Association took the initiative in making requests to the government, and managed to avoid the problem. It is essential for us to be able to use public statistics to conduct the Life Span Study and other studies. In order to conduct a long-term epidemiological study in connection with the Fukushima Dai-ichi nuclear power plant accident, access to public statistics is also essential. In that sense, I may have made some contributions worthy of a Distinguished Service Award from the Japan Epidemiological Association.

Crystal plaque presented by the Japan Epidemiological Association

Mini-workshop "Roles of Smoking on Radiation Risk of Lung Cancer"

Nori Nakamura, Chief Scientist

A mini-workshop titled "Roles of smoking on radiation-risk of lung cancer" was held in the RERF Auditorium on the afternoon of February 4, 2011. The workshop was organized in response to the proposals by Dr. Michiaki Kai (Oita University of Nursing and Health Sciences) and Dr. Ohtsura Niwa (formerly with National Institute of Radiological Sciences). It was motivated by a controversy over possible interpretation of higher risk of lung cancer among smokers with the same radon concentration, which had resulted from reassessment of radon effects by the International Commission on Radiological Protection (ICRP) in 2009, and by a finding last year (paper by Furukawa *et al.*) suggesting higher risk of lung cancer attributable to radiation among A-bomb survivors who smoke (excluding heavy smokers) than among the survivors who do not. We also hoped to understand interactions between radiation and smoking at the cellular (stem cell) level.

Dr. Okubo's welcome address was followed by the presentations "Trends of lung cancer in Japan" by Dr. Kotaro Ozasa (Chief, Department of Epidemiology), "Joint effects of radiation and smoking on lung cancer among atomic-bomb survivors" by Dr. Kyoji Furukawa (Department of Statistics), and "Pilot study: Genetic and epigenetic alterations in lung cancer among atomic bomb survivors" by Dr. Masataka Taga (Department of Radiobiology/Molecular Epidemiology). After a short break, the session resumed and Dr. Yuichi Ishikawa (Cancer Institute of Japanese Foundation for Cancer Research) spoke on "Present status of lung cancer in Japan: Characteristics of Japanese lung cancer and genotype-phenotype correlations," Dr. Michiaki Kai on "Multistage carcinogenesis and lung cancer risk," Dr. Suminori Akiba (Kagoshima University) on "Indoor radon and lung cancer risk," and Dr. Charles Land (formerly with U.S. National Cancer Institute) on "Comments on radiation cancer risk in

smokers and nonsmokers compared with previous risk." The presentations were followed by a general discussion that concluded the event.

The findings already elucidated are as follows:

1) Non-smokers develop lung cancer, although at a lower rate. The majority of such lung cancer is said to be adenocarcinoma occurring in the lung periphery.
2) Earlier, it was mentioned that risks for squamous cell carcinoma (SCC) and small cell carcinoma (SmCC) developing in the central region of the lungs increase among smokers. However, adenocarcinoma is recently on the increase (which is hypothesized as attributable to improved filters).
3) Not all smoke particles from cigarettes infiltrate deeply into the lungs.
4) The risk increase from radiation exposure in SmCC is observed both in A-bomb survivors and in radon miners (Land's 1993 paper).
5) Smoking and radiation enhance each other's effects (synergistic effects).
6) Radon is absorbed into the lungs not only in the form of a gas, but also in the form of solids attached to atmospheric dust particles. The range of its α particles is short. Therefore, it would be difficult to assess which parts of the lung are affected by radon. (If stem cells are located several layers of cells deep below the surface of the respiratory tract, they might not be exposed to radiation.)

Taking the above points into consideration, I gave some thought to possible interactions between smoking and radiation.

A-bomb radiation effects: A-bomb radiation affected the entire lung uniformly. The lung cancer subtype that increases with radiation exposure is said to be SmCC. Therefore, it seems likely that SmCC is as sensitive to radiation as it is to smoking, and conversely that SCC and adenocarcinoma are less sensitive to radiation.

Effects of radon α particles: The lung cancer subtype that is increased by radon exposure is said to be SmCC, which means that α particles from radon and its daughter nuclides reach stem cells, the originating point of SmCC. The lower risks for SCC and adenocarcinoma can be explained by lower radiosensitivity even if radon α particles reach stem cells.

Interactions between radiation and smoking: Whether exposure to A-bomb radiation or to radon, effects are greater when radiation and smoking are combined than when each exerts effects independently (1 + 1 > 2; i.e., joint effects are greater than their simple additive effects). However, risk from smoking is far greater than that from radiation, meaning that radiation is not smoking's equal. Looking at this from the viewpoint of radiation effects, although SmCC is not the most prevalent subtype of lung cancer attributable to smoking, it is still affected by smoking as its effects are that much stronger. Because radiation and chemical compounds in tobacco smoke exert different kinds of damage on DNA and have different cell stimulatory effects, radiation and tobacco smoke probably complement each other's weaknesses during the multistage process of carcinogenesis.

At the mini-workshop, I learned that percentages of various lung cancer subtypes differ between the Japanese and Caucasians and that smoking effects are smaller among Japanese than among Westerners. I felt as if I was learning the history of smoking in the 20th century in various countries. I had a great time, seeing Dr. Land after a long time, and engaging in lively discussions. Above all, I became interested in knowing whether or not the latest Life Span Study data will support the conclusion made by Dr. Land in his above-mentioned paper published in 1993, which is now almost 20 years ago (i.e., the lung cancer subtype increased by radiation exposure is SmCC).

Lastly, I would like to take this opportunity to express my appreciation to all those who helped me organize this workshop.

Participants of the mini-workshop titled "Roles of smoking on radiation risk of lung cancer"

Workshop on Potential Extensions to DS02 Organ Dose Calculations

Harry M. Cullings, Chief, Department of Statistics

One of the notable strengths of RERF's studies is their dosimetry—estimation of the radiation doses received by survivors, without which study results cannot be stated in terms of risk or effect per unit dose for use in radiation protection. A series of dosimetry systems for calculating survivors' doses based on their detailed location and shielding information have been developed over the last sixty years by international scientific working groups, culminating in Dosimetry System DS02. One of the hallmarks of DS02, and its predecessor DS86, is that they calculate detailed dose estimates for particular organs and tissues of the human body, which can differ substantially with an organ's effective depth in the body, especially for the dose from neutrons. DS02, however, uses the same organs and organ dose computational methods as DS86, which reflect the state of knowledge and computing power that were available in the early 1980s. DS86 and DS02 calculate dose only to certain organs, which were chosen in light of the understanding of radiation biology in that time period, and were limited to fifteen organs for practical reasons. For other organs and tissues it has therefore been necessary to choose surrogates from among the 15 organs to provide rough estimates of dose. Moreover, it has been recognized in recent years that there has been an explosion of detailed three-dimensional anatomical data on the human body from medical imaging technologies, and that computing power is much greater than it was some thirty years ago.

The above considerations suggested that it would be useful to explore ways to take advantage of the great effort expended on DS02, by using the detailed radiation fields that it calculates at individual survivors' locations, with new organ dose modules to calculate dose to a wider variety of organs with improved accuracy. Many of the aspects of such improved calculations could utilize resources that are already available in the radiation protection community, including Monte Carlo computational packages and methods for developing detailed models of the human body. On February 23 and March 7–8, 2011, the "International Workshop on Potential Improvements to Organ Dose Calculation for the Atomic Bomb Survivors Using DS02" was held at the Hiroshima Laboratory. In addition to two RERF speakers, the workshop included six speakers from four Japanese research institutes and universities (National Institute of Radiological Sciences, Japan Atomic Energy Agency, Kyoto University Reactor Research Institute, and Hiroshima University) and five speakers from international agencies and universities (Helmholtz Institute Munich, Health Canada, Science Applications International Corporation, Oak Ridge National Laboratories, and Vanderbilt University).

The purpose of the workshop was to discuss some key needs for improved organ dosimetry and the practical means by which the organ dose calculations of the DS02 dosimetry system could be improved. There are a number of organs for which specific dose estimates are desirable but not currently available. Special meetings were held in connection with the workshop to discuss the technical issues involved in biodosimetry measurement of radiation dose using electron spin resonance (ESR) on donated teeth and the need to obtain accurate DS02 calculations of dose to tooth enamel for comparison to measurements. As DS86 and DS02 include only three models of the human body for different age categories, there is a need for better modeling of the body at various ages during childhood and adolescence. Another need is for gestational age-specific doses for survivors who were exposed *in utero*. The workshop ended with focused discussions of what methodologies, software, and models of the human body should be used and adapted to the Japanese population of the 1940s, and the participants agreed to collaborate on developing a new series of models for improved calculations. Short papers based on the proceedings of the workshop will be published in a special issue of the journal *Radiation Protection Dosimetry*.

Workshop on potential extensions to DS02 organ dose calculations held at Hiroshima Laboratory

Highlights of RERF Departments: Research Activities in the Department of Epidemiology

Kotaro Ozasa[1] and Akihiko Suyama[2]

Departments of [1]Epidemiology (Hiroshima) and [2]Epidemiology (Nagasaki), RERF

Abstract

The principal focus of the research program of the Department of Epidemiology is to study the effects of ionizing radiation in the Hiroshima and Nagasaki survivors of the atomic bombings and their children through mortality and cancer incidence studies. Several fixed cohorts—the Life Span Study (LSS) cohort consisting of about 120,000 A-bomb survivors, the *in utero* cohort consisting of about 3,600 persons who were *in utero* at the time of the bombings, and the children of A-bomb survivors (F_1) consisting of about 77,000 persons—have been established to accomplish the purpose. They have been followed up for their deaths in all of Japan and for cancer incidence in Hiroshima and Nagasaki. Histological specimens of cancer cases are also collected by the tissue registries in collaboration with community pathologists. Mail surveys have been conducted periodically and provided information on lifestyle and other factors that may confound or modify the effects of radiation.

Periodic reports of the radiation effects of LSS mortality and cancer incidence data have been released, and considerable research has been conducted on various aspects of the data and using additional information from histological diagnoses and mail surveys. *In utero* and F_1 cohorts have been studied as well. The information on the cohort members has been provided to all departments of RERF for their research activities. It is important to harmonize the epidemiological evidence with biological mechanisms of radiation effects. Many studies in the department have been conducted in collaboration with various researchers inside and outside RERF. International risk assessment groups use the cohort study results as the primary basis for radiation risk estimation, such as the U.S. National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR VII, 2005), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2006), and the International Commission on Radiological Protection (ICRP). RERF has vigorously managed the Hiroshima and Nagasaki tumor/tissue registries. The data have long been included in the "Cancer Incidence in Five Continents" (by the International Agency for Research on Cancer [IARC]/the International Association of Cancer Registration [IACR]), a compilation of worldwide cancer incidence data, and are given the highest rating by that consortium.

At the end of 2006, 85% of the LSS cohort members who were under 10 years old at the time of the bombing, 89% of *in utero,* and 90% of the F_1 cohort were still alive. Therefore, continued follow-up of those young-age groups for an additional 20 years or more is clearly essential. In this article, recent research activities and future perspectives of the department are discussed.

Research Scientists of Hiroshima Epidemiology (first row from left) Ritsu Sakata, Hiromi Sugiyama, Kotaro Ozasa (department chief), Yukiko Shimizu, (second row from left) Eric J. Grant, Truong-Minh Pham, Ayako Takamori (visiting student fellow)

Research Scientists of Nagasaki Epidemiology (from left) Midori Soda, Akihiko Suyama (department chief)

Department Staff

The Department of Epidemiology, Hiroshima, currently is comprised of a chief, two associate senior scientists, one research scientist, one post-doctoral scientist, two visiting scientists, and one visiting student fellow. The Department of Epidemiology, Nagasaki, includes a chief and one research scientist.

Research Projects and Recent Progress

1. Life Span Study (LSS)

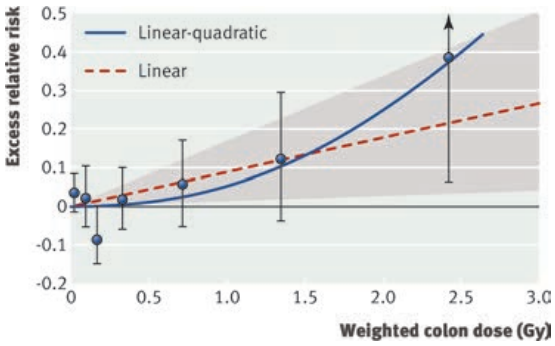
Evaluation of the late health effects of radiation derived from the atomic bombs is RERF's most important goal. It requires unbiased analysis and reporting as well as careful and complete follow-up of people who survived the atomic bombings. The LSS cohort consists of a representative population of survivors in Hiroshima and Nagasaki who have been followed up since 1950. Subjects of the study consist of 93,000 A-bomb survivors who were selected from a nationwide A-bomb survivors survey conducted in 1950 and 27,000 persons who were not in Hiroshima or Nagasaki at the time of the bombings (not-in-city group [NIC]), but who were residents of either city in 1950. The subjects were asked about their location, shielding at the time of the bombings, and other related issues (Master Sample Questionnaire) and individual doses were subsequently estimated. Dose estimates are periodically refined. The latest revision of the dosimetry system, DS02, was released in 2003.

The subjects' survival status is periodically checked using the *koseki* (family registration system) that has virtually complete death ascertainment. The cause of death is obtained from death certificates kept at public health centers throughout Japan. Cancer incidence is available from the cancer registries within Hiroshima and Nagasaki prefectures. Information on leukemia was collected independently through a special leukemia registry kept by area hematologists until 1987. The LSS cohort also serves as the sampling frame for the Adult Health Study (AHS) clinical subcohort.

At the end of 2006, 39% of LSS subjects, including 85% of those exposed before age 10, were alive, so continued follow-up is essential. Analyses of interactions between radiation and smoking will be considered for smoking-related cancers and for other diseases. Estimation of radiation risks at low-to-moderate dose levels will be considered by including lifestyle factors and geographic factors to help interpret the fluctuations of estimated risk at low-dose levels. Because of high public interest, issues of residual A-bomb radiation exposure will be examined in coordination with the RERF Dosimetry Committee, although only limited individual information is available.

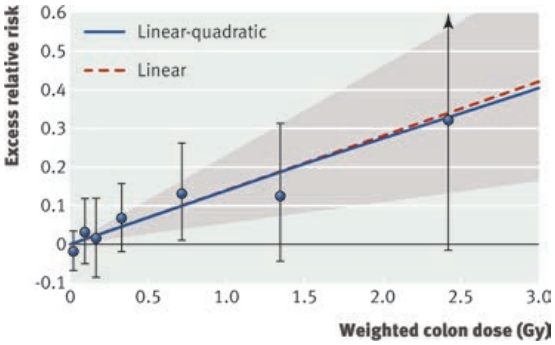
Radiation risk of cancer and non-cancer diseases

Periodic reports of radiation risk on the LSS have been released along with many more publications on various aspects of the data.[1,2] Analyses of updated cancer and non-cancer mortality data through 2003 using the DS02 were completed and a manuscript was recently submitted to a scientific journal. Analyses of specific diseases including leukemia,[3] malignant lymphoma[4] (in collaboration with University of North Carolina), and malignant tumors in bone and soft tissue[5] have been published. Analyses of mortality from cardiovascular diseases have been published (Figures 1 and 2)[6] and those for non-cancer respiratory and digestive diseases are being conducted. A study of the best model to fit radiation risk and non-cancer mortality was completed and a study of influences of co-morbidity from cancer and non-cancer diseases on



Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles.

Figure 1. Radiation risk of stroke (cited from ref. 6)



Radiation dose-response relation (excess relative risk) for death from heart disease, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles.

Figure 2. Radiation risk of heart disease (cited from ref. 6)

the observed radiation effects upon mortality from various diseases is beginning in collaboration with Kurume University.

Mail surveys and utilization of the data

Mail surveys have been conducted periodically (1965, 69–70, 79–80, and 91–92), which provide information on lifestyle and other factors that may confound or modify the effects of radiation. The following are studies of evaluation of radiation risk using mail survey data. Many of them were conducted in collaboration with other institutions including the Radiation Research Partnership (with the University of Washington and Kurume University) and the University of Rochester.

- Age at menopause was significantly earlier in women with high-dose radiation exposures.
- Urothelial cancers showed strong independent associations with smoking and radiation. No effect modification or confounding was observed in the radiation effects due to smoking or other lifestyle factors.
- Potential confounding or interaction of anthropometric factors with radiation on colon cancer incidence was examined, but there was no evidence that sensitivity to the effects of radiation on colon cancer risk depended on body mass index (BMI).
- The radiation-associated risk of breast cancer does not vary significantly by reproductive status (menarche and first birth) at the time of the bombings, but is influenced by age at irradiation.
- Esophageal cancer at the lower anatomic segment and cases of diffuse gastric cancer showed a high dose response with radiation. Smoking was shown to be the most important modifiable risk factor.[7]
- Chronic renal failure showed a significant association with radiation. Adjustment for self-reported hypertension and diabetes improved the model fit but did not substantially change the excess relative risk (ERR) estimate.

A new mail survey

A new survey is required, not only to update the information as more than 15 years have passed since the last mail survey in 1991, but also to collect new information on exposures to radiotherapy and relatively high-dose diagnostic radiation procedures (e.g., CT scans). In addition, participants in the clinical health study have been solicited through this mail survey from the LSS subjects who were younger than 10 years old at the time of the bombings. As of March 31, 2011, 11,863 subjects responded to the questionnaire.

Population for cancer incidence studies

Since the cohort members in cancer registry areas have not been directly contacted, the numbers of cohort members for cancer incidence studies in the LSS were estimated using migration information from the AHS subjects by time, age, gender, and city and are now being reviewed and updated in collaboration with the Department of Statistics. A similar approach will be necessary for those in the *in utero* and F_1 cohorts.

Other research topics

Risk of second primary cancers associated with radiation was evaluated in collaboration with the University of Washington in the Radiation Research Partnership. The radiation-related ERRs were approximately the same for first and second cancers as illustrated in Figure 3. Radiation dose was most strongly related to the risk of solid tumors that are considered to be more radiation sensitive, including second primary lung, colon, female breast, thyroid, and bladder cancers (Table).[8] The incidence of multiple primary cancers is also being evaluated in Nagasaki survivors in collaboration with Nagasaki University. Secondary cancer risk of a subset from the LSS who had undergone radiotherapy subsequent to A-bomb radiation is being evaluated in collaboration with the Japan National Institute of Radiological Sciences. The effects of smoking on mortality among the LSS population have been estimated using methodologies in collaboration with Oxford University because it has been suggested that the effects of smoking on mortality in the Japanese population is smaller than elsewhere.

2. *In Utero* Cohort Study

The LSS initially did not include those with *in utero* A-bomb exposure, but since data from the Oxford Childhood Cancer Study suggested that the fetus might be especially sensitive to radiation, it was decided to study them as a special group. The *in utero* cohort was defined on the basis of a roster

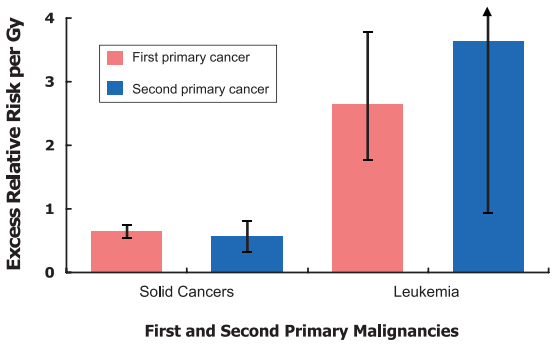


Figure 3. Radiation risk for first and second cancers (cited from ref. 8)

Table. Relationship between estimated radiation dose and risk of first and second primary cancers (cited from ref. 8)

Solid tumors

Colon dose (Gy)	Person years for time to first cancer	No. of first primary cases	RR* (95% CI)	Person years for time to second cancer	No. of second primary cases	RR* (95% CI)
<0.005	943,630	5,580	1.00 (reference)	25,227	401	1.00 (reference)
0.005–0.49	1,056,910	6,424	1.03 (0.99–1.07)	30,045	475	1.01 (0.88–1.15)
0.50–0.99	82,759	700	1.42 (1.31–1.54)†	3,757	55	1.01 (0.76–1.33)
1.00–1.99	41,770	474	1.92 (1.74–2.10)†	2,146	62	1.98 (1.51–2.59)†
≥2.00	13,923	188	2.53 (2.19–2.93)†	1,078	38	2.47 (1.77–3.46)†
ERR/Gy*			0.65 (0.57–0.74)†			0.57 (0.36–0.82)†

*RR and ERR/Gy are adjusted for sex, city, attained age, age at time of bombing, and age at first cancer diagnosis (second primary cancer risk estimates only).
†$P < 0.05$.

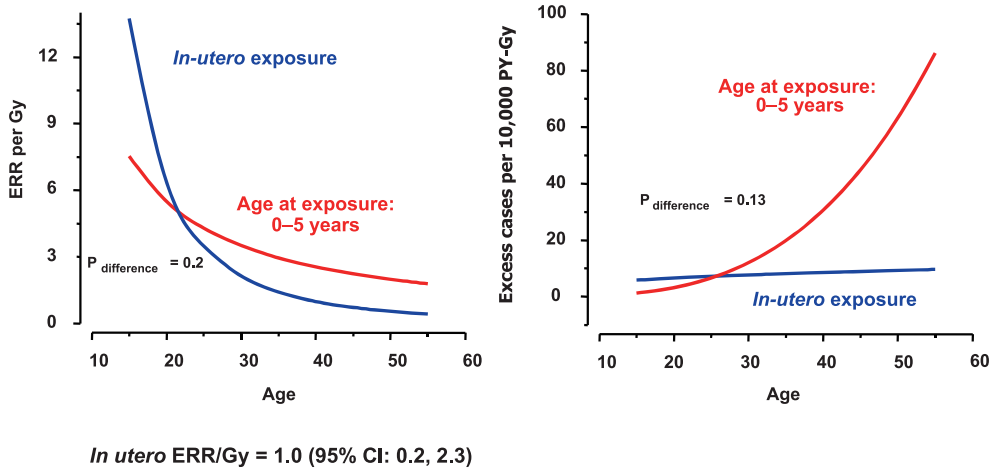
of people born between the day of the bombing and 30 June 1946. Vital status and causes of death for the 3,600 people in this cohort have been determined through routine, periodic checks of *koseki* records using the same procedures as for the LSS. The most recent cancer incidence paper with larger numbers of cases suggested a different temporal pattern of excess between the *in utero* and younger LSS cohorts, and that the excess risk following *in utero* exposure appeared to be somewhat smaller than that seen in those exposed as children (Figure 4).[9] Analysis of the mortality data for 1950–2003 has almost been completed.

3. F_1 Cohort Study

The purpose of the study is to ascertain the long-term health effects among the children of parents who were exposed to radiation. A cohort of the children of A-bomb survivors (F_1) was selected from the children born from May 1946 through December 1984 to parents with a variety of A-bomb radiation exposures ranging from those known not to be in the city at the time of the bombing to those who were heavily exposed. The F_1 cohort sample consists of 76,814 subjects. The subjects' survival status, cause of death, and cancer incidence have been obtained by the same methods used for the LSS subjects. Neither cancer incidence nor cancer or non-cancer mortality was significantly associated with paternal or maternal gonadal dose[10,11] (see also Figure 5). As of the end of 2006, 90% of the F_1 cohort were still alive and the average age was 49.6 years old. Analysis of the mortality data for 1950–2003 has almost been completed.

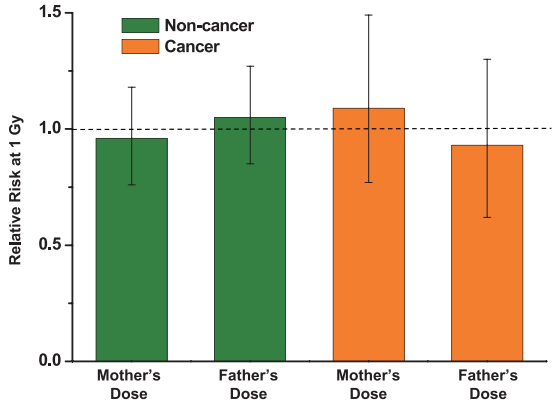
F_1 mail survey

This survey was primarily designed to ascertain baseline epidemiological data on the F_1 subjects, and secondarily to identify F_1 cohort members willing to participate in clinical health examinations in order to investigate possible relationships of parental radiation doses to adult-onset diseases in the F_1 cohort. Among the F_1 cohort, 24,673 members were selected, whose *koseki* and current address were in the AHS catchment areas plus a small number of children of high-dose parents whose *koseki* was outside the catchment area but whose current address was in the catchment area. The survey was carried out between 2000 and 2006. At the end of the survey, 16,756 subjects responded. A total of



***In utero* ERR/Gy = 1.0 (95% CI: 0.2, 2.3)**

Figure 4. Solid cancer risk patterns for *in utero* and childhood exposure in A-bomb survivors (cited from ref. 9)



To date, the frequencies of cancer and other diseases in the offspring are unrelated to parental radiation dose, but 20–30 more years of follow-up are needed to provide definitive evidence (Suyama *et al.*, unpublished).

Figure 5. Relative risk for non-cancer and cancer mortality in 41,000 offspring of atomic-bomb survivors, 1946–2003

11,951 (71% of questionnaire respondents) actually participated.[12] The information of the mail survey data was used as covariates and published in the report of F_1 clinical study analysis, investigating possible associations of parental radiation dose to F_1 multifactorial diseases.[13]

4. Hematological Studies in LSS

The program is designed to document all cases of leukemia, and certain closely-related hematologic diseases like multiple myeloma, lymphoma, polycythemia vera, myelofibrosis, aplastic anemia, or myelodysplastic syndrome (MDS). A recent study examined the radiation risk of MDS in Nagasaki during 1985–2004 in collaboration with Nagasaki University and the Statistics Department. The ERR at 1 Gy was 4.27 (95% confidence interval 1.63–9.48). The MDS risk was significantly greater among those exposed at younger ages (Figure 6)[14] Another study of comprehensive analyses for leukemia and related diseases is being conducted in collaboration with the Statistics Department.

5. Site-specific Special Cancer Studies in LSS

The tumor and tissue registries of Hiroshima and Nagasaki prefectures are functioning well and permit pathologists and epidemiologists to confirm tissue diagnoses and clinical records and expand the incidence studies with site-specific surveys, case-control studies, etc. Certain pathologists at collaborating hospitals and institutes have worked extensively with RERF, to maintain uniform protocol and analysis procedures. There are three major areas of study effort to be undertaken: case ascertainment, pathological review, and data analysis. Sources of cancer cases are population-based tumor and tissue registries in the Hiroshima and Nagasaki areas, RERF autopsy series, death certificates, site-specific tumor registries, RERF records gathered in the past, and others. Information and materials on possible cases are collected from those sources. First, the pathologists reviewed the information on paper and selected probable cases of target cancer ('the first screening'). For the probable cases, the pathologists may jointly or independently (blindly) review the materials. If two or more review results are consistent, they are accepted. If they disagree, the panel meets jointly to review the cases.

Site-specific special cancer studies have been conducted for various cancers and/or tumors. Those studies are conducted in strong collaboration with the U.S. National Cancer Institute (NCI) and with the Statistics Department, and also with Hiroshima and Nagasaki Universities and associated local hospitals. At present, studies for liver, salivary glands, and central nervous system are completed, and are underway for skin, ovary, thyroid, breast, lung, lymphoid system, uterus, and soft tissue and bone. For examples, a pathology paper on the characteristics and radiation risk of papillary microcarcinoma was published.[15] For lung cancer, both smoking and radiation exposure appeared to significantly increase the risk of each of the major lung cancer histologic types.[16]

6. Hiroshima and Nagasaki Tumor/Tissue Registries

Population-based tumor registries have been active in Hiroshima since 1957 and in Nagasaki since 1958, and conducted by the methods of abstracting medical records and notifications from hospitals and clinics at present. Population-based tissue registries were established in Hiroshima and Nagasaki in 1973 and 1974, respectively. The tis-

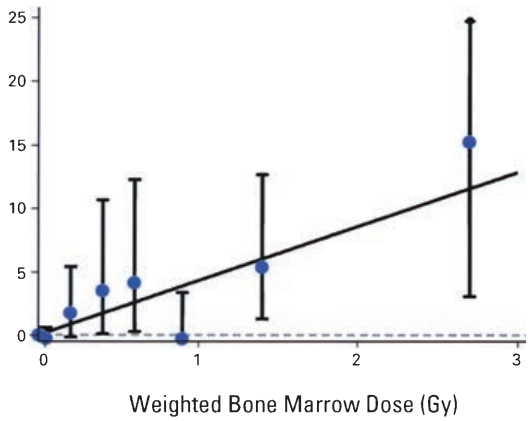


Figure 6. Sex- and age-adjusted radiation dose-response for MDS (cited from ref. 14)

sue registries are collecting the pathology reports and representative HE-stained slides of cancer cases.

The integrated data of tumor and tissue registries have long been included in "Cancer Incidence in Five Continents" (by IARC/IACR), a compilation of worldwide cancer incidence data, and are given the highest rating by that consortium. Local activities of the registries have been reported by department members.[17–19]

7. Pathology Studies

A Pathology Program has been conducted since the inception of ABCC. During the early years of ABCC, it consisted almost entirely of an autopsy program in the cities of Hiroshima and Nagasaki, with emphasis on the procurement of autopsies of exposed individuals, but with later modifications to include controls and to enhance its epidemiologic usefulness. It proved extremely useful to verify mortality information, and it permitted the study of possible radiation-induced tissue damage. However, because the autopsy rate declined after the early 1960s, it was terminated in 1987, and a revised research plan based primarily on surgical specimens was initiated.

We are taking an inventory of the formalin-fixed paraffin-embedded tissues stored in the Department of Epidemiology, which will be computerized to facilitate future specimen utilization. Those specimens are from around 7,000 autopsies or surgical operations. To maintain LSS surgical samples that have been kept in local hospitals, a new research project of "Development of an archival system for surgical cancer samples from A-bomb survivors" is being initiated in collaboration with Hiroshima and Nagasaki Universities and local hospitals.

Collaborations

The Epidemiology Department collaborates with the Clinical Studies Department in sharing data on disease risk factors, mortality data, etc.[20] and in conducting the mail surveys that have recruited subjects for the F_1 clinical study and the expansion of the clinical AHS. It is collaborating with the Departments of Genetics and Radiobiology/Molecular Epidemiology for the investigation of pathological specimens of breast and thyroid cancers, and with the Statistics Department in study-design and data-analysis efforts. Furthermore, the information on the LSS, *in utero,* and F_1 cohort members has been provided to all departments of RERF for their research activities.

The Department of Epidemiology also has an extensive network of outside collaborations, including multiple collaborative studies with the U.S. NCI, the Radiation Research Partnership (University of Washington and Kurume University), Oxford University, the National Institute of Radiological Sciences, Kyushu University, University of Occupational and Environmental Health, and other researchers in various universities. In collaboration with Hiroshima and Nagasaki Universities and local hospitals, pathological programs, including site-specific cancer studies and storage of surgical specimens, are performed. Also we are collaborating with the Asia Cohort Consortium, a prospective study of numerous combined cohorts that include over one million Asians to assess the effects of lifestyle factors on cancer risks.

Future Studies

The major future activities of the department will be to:

1. Continue to follow-up the LSS, *in utero,* and F_1 cohorts and publish updated estimates of radiation risks for mortality of cancer and noncancer diseases as well as cancer incidence. Those studies will increasingly focus on the LSS subjects who were young at the time of the bombings. Also, covariate data from the LSS mail surveys will be utilized to evaluate other risk factors for confounding or modification of radiation risk.
2. Focus on radiation effects at low-dose levels of initial radiation exposure, considering sources of dose uncertainties, confounding and effect-modification factors such as lifestyles and geographic distribution of the subjects. The indirect A-bomb radiation effects by early entrance after the explosions and bomb fallout ("black rain") will be considered, although limited information is available.
3. Continue the site-specific cancer studies and the hematological study with histological/hematological reviews within the LSS and publish those results.
4. Establish a system to preserve pathological specimens derived from the LSS, *in utero,* and F_1 cohorts in collaboration with hospitals and universities in Hiroshima and Nagasaki areas.
5. Continue the management of the Hiroshima and Nagasaki tumor/tissue registries in order to support the fundamental core studies.

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Highlights of RERF Departments: Research Activities in the Department of Statistics

Harry M. Cullings

Department of Statistics, RERF

Abstract

The Statistics Department develops and implements methods for radiation risk estimation and provides statistical consulting support to RERF researchers in study design, data quality assurance, and data analysis. In addition, the department implements a dosimetry system for calculating survivors' radiation doses and maintains a database of survivor dose estimates, presently using the DS02 system provided by a combined external and internal scientific working group, and provides key statistical and dosimetric support to RERF projects in biodosimetry. The department's research activities relate to the selection and adaptation of appropriate biostatistical methods, or development of new methods, and their application to RERF's epidemiological, clinical, and basic sciences data.

The Statistics Department has historically led in the development of analytical methods for major aspects of the RERF research program such as risk estimation. This includes not only the development of tools such as Poisson regression but methods to handle various problem areas in follow-up data of major RERF cohorts, such as dose uncertainty, undocumented out-migration of cohort members from cancer tumor registry catchment areas, and missing data on smoking and other potentially confounding risk factors apart from the radiation doses received directly from the atomic bombs. The department also develops methods for analysis of longitudinal data from the Adult Health Study,[1] which involve repeated measurements on the same individuals over time, with inevitable changes in laboratory methods, instrumentation, and the items being measured that correspond to changes in medical science and technology.

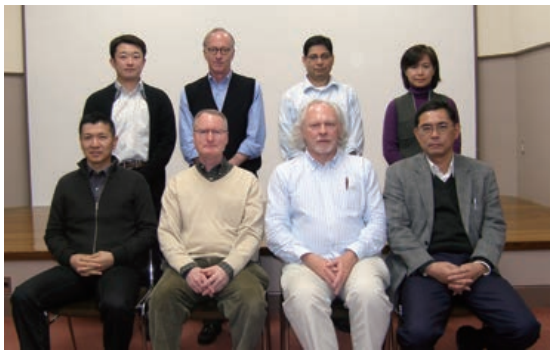
The valuable and limited nature of RERF's biosample resources leads to special requirements for related studies. Researchers in Statistics evaluate and develop special methods of sub-cohort sampling for various special clinical studies, such as nested case-control studies of cancer, radiation effect modification using serum biomarkers, or molecular epidemiology studies of the immunogenome and cancer susceptibility in response to radiation. Statisticians also develop many special methods to meet the requirements of RERF's basic science research in genetics, immunology, radiation biology, and molecular epidemiology. This increasingly requires methods for analysis of high-dimensional data being generated by technologies such as microarrays that provide large numbers of measurements on a single sample.

Dosimetry is an active area of research at RERF, and the Statistics Department collaborates actively with researchers in the Epidemiology Department on the improvement of survivors' exposure data and the evaluation of potential individual and population exposure from residual radiation after the bombings, and with researchers in the Genetics Department on the important data from biodosimetry such as chromosome aberration analyses and electron spin resonance analyses of teeth.

Unlike other departments, the Statistics Department provides structured and extensive consulting services to other departments, in addition to doing its own research. Given the crucial importance of sound statistical advice in the design, analysis, and conduct of studies, the department tries to take a proactive approach to consulting, beginning with early involvement in study design, and devotes a majority of its staff's effort to consulting.

Department Staff

The Statistics Department currently comprises the chief, assistant chief, two senior scientists, an associate senior scientist, three research scientists, two research assistants, and an administrative assistant.



Research Scientists of Statistics (first row from left) Kyoji Furukawa, John B. Cologne, Harry M. Cullings (department chief), Eiji Nakashima (second row from left) Munechika Misumi, Robert D. Abbott, Ravindra Khattree, Wan-Ling Hsu

Research Areas

Risk Estimation Methodology

A major focus of the department's research in methods of risk assessment is the use of individual data, which allows advantages over use of grouped data as are used in methods such as Poisson regression. Potential advantages include improved ability to incorporate mechanistic hypotheses, model missing-data mechanisms, examine the shape of the dose response, and account for uncertainties in dose estimates. Those advantages come at a cost: the need to evaluate integrals of complicated likelihood functions such as those of Bayesian models provides a computational challenge due to the sheer number of calculations involved in methods such as Markov Chain Monte Carlo (MCMC) approximations, that has not yet been overcome for most of the data sets of interest. As part of an interim solution to the particular problem of missing data, research has been initiated on the technique of multiple imputation, and a manuscript has been prepared on its use for missing smoking data in risk estimation of radiation and lung cancer.

The department continues to collaborate with investigators at the U.S. National Cancer Institute Radiation Effects Branch, resulting in three published papers this past year and involvement in several new research projects. A recent paper from this collaboration involves the application of generalized additive and multiplicative risk models to more fully investigate the interaction between smoking and radiation in development of lung cancer (Figure 1).[2]

Another area of interest is the radiobiological effectiveness (RBE) of neutrons. This is motivated by recurring concerns about how neutron dose should be treated, i.e., by particular weighting, in RERF's major studies, as well as other fundamental concerns in radiation biology. The department recently began collaborating with a senior former RERF investigator and plans a manuscript on the results of attempting to estimate an optimal weight for neutron dose in risk regression using RERF cancer mortality data.

Another avenue of basic statistical research related to the use of individual data concerns methods for studies in which outcomes such as cancer are treated as survival (time to event) type data and analyzed by Cox regression. A member of the department performed research on choice of time scales, i.e., age vs. time since study inception, in Cox regression of epidemiologic follow-up data, and presented methods and recommendations in an RERF colloquium. The department also collaborated with investigators at the National Taiwan University to create a statistical research protocol (RP) to test a new semi-parametric survival extrapolation model using RERF data.

Finally, geospatial methods can play an important role in RERF studies. They can check in detail the usual assumptions of spatial uniformity, across the study area, of baseline rates of the health outcomes under study, providing a basis for hypotheses that can be investigated further in regard to causes of any patterns that are found. Such investigations can address concerns being raised by external investigators about putative sources of undocumented exposure to residual radiation. They are also highly relevant to emerging concerns about the ability to quantify "low dose" risk. A manuscript on geospatial analysis of cancer incidence in the Life Span Study has been prepared[3] and an RP and other manuscripts are being planned.

Causal Models

Causal models apply to situations in which a measurable risk factor is thought to lie on a causal pathway between 1) radiation and other "exogenous" risk factors and 2) the health outcome of interest. The department has collaborated with Kurume University in developing an RP on causal modeling applied to radiation, inflammation, and

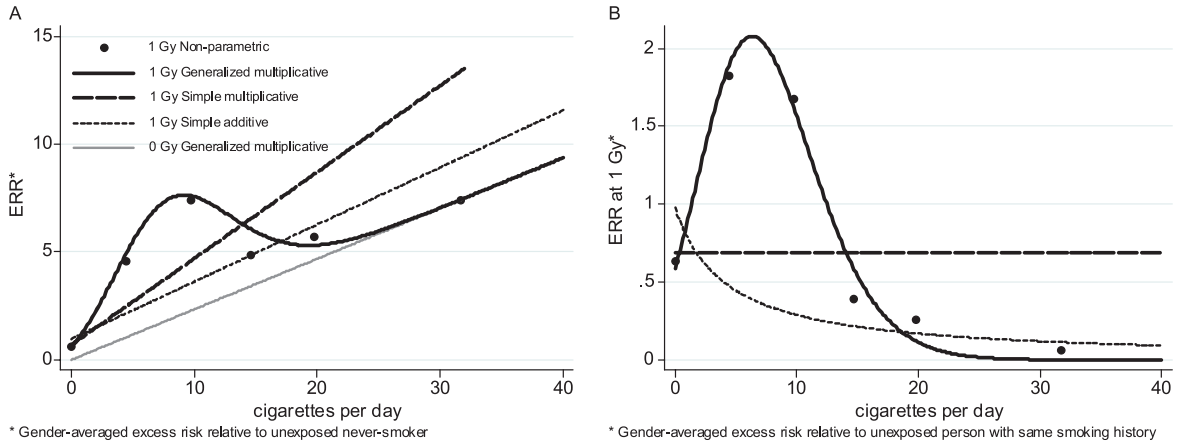


Figure 1. Radiation risk of lung cancer for different levels of smoking

cataracts, and is more generally interested in finding ways to address the question of intermediate risk factors. The department recently had a new statistical RP approved on specialized methods of intermediate risk factor analysis for stratified (counter-matched) nested case-control sampling designs used in RERF studies. (This also relates to the next topic of special study designs.)

Special Sub-cohort and Two-stage Study Designs

In addition to the causal modeling just mentioned, other aspects of sub-cohort designs are being actively researched. Recent work has included an evaluation of statistical efficiency vs. sub-cohort sampling fraction for case-cohort designs (Figure 2), and the need in such studies to think of them as two-stage studies and correct for the distribution in the sub-sample of variables that are known only in the sub-sample, using information from their relationship to variables that are known for the full cohort, which was presented at an RERF colloquium. Members of the department also produced an S-plus (statistical software) program to perform the "swapper" algorithm for stratified case-cohort data (such as those collected in the radiobiology/molecular epidemiology study of immunogenes and cancer) as a springboard toward eventually writing an R function to add to the publicly available (freeware) R package for survival analysis, which lacks this needed capability due to the algorithmic complexity.

Mechanistic Modeling of Carcinogenesis

The Statistics Department has ongoing collaborations with external investigators interested in mechanistic modeling of carcinogenesis and leukemogenesis, at the Dutch radiation protection institute (RIVM) and at the Helmholtz Institute in Munich (HIM), Germany.[4] Both groups are interested in two-stage type models that allow for clonal

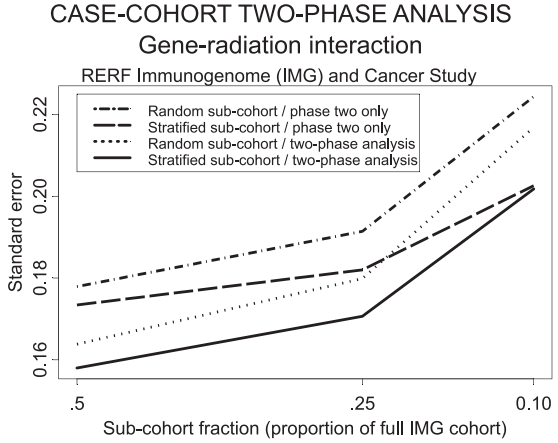


Figure 2. Effect of sub-cohort fraction in case-cohort designs

expansion of cells in intermediate stages. The department continued to support a collaborative research project on modeling of leukemia with investigators from RIVM, with a manuscript in preparation, and collaborated on a manuscript on mechanistic vs. descriptive modeling of solid cancer and multi-model inference with investigators from HIM.[5]

Dosimetric Uncertainty

The problem of uncertainty in the dose estimates of survivors has been a statistical problem of concern for many years at ABCC and RERF.[6,7] The Statistics Department has continued to actively collaborate with a former investigator who made major contributions to theory and methodology on the adjustment of dose estimates to correct for the effect of dose error under an assumed error model,[8] with the collaboration focusing most recently on treatments that distinguish different types of error [9] and possibly different classes of survivors with different error distributions, and simulations to determine the effect on risk estimation of detailed statistical assumptions about errors in dose. In addition, the department has entered into several new collaborations with external investigators who are interested in using biodosimetry data to develop information on dose uncertainty. In the last year, a completed RP and an external funding award from the U.S. National Institute of Health have been achieved by one of the groups from the Fred Hutchinson Cancer Research Center in Seattle, Washington, for a semi-parametric approach with minimal assumptions about the statistical form of the dose uncertainty, using partial (on part of the cohort) biodosimetry data. Another RP is nearing completion, with a group from the University of Buffalo in New York, on an instrumental variables approach to dose error that utilizes a more explicit statistical error model. Finally, a new RP is in preparation with a group from the University of Southern California, on joint modeling of radiation dose estimates, chromosomal aberrations, and early (e.g., epilation) as well as late (e.g., cancer) effects of radiation. (The latter project also relates to the previous item on causal modeling, and all of the three new external collaborations just mentioned relate to the next item: biodosimetry.)

Biodosimetry

In addition to being interesting in their own right, biodosimetry results have great value in evaluating the uncertainty in survivor dose estimates from the dosimetry systems (i.e., DS02), which are based on reported information about survivors' location and shielding at the time of the bombings. While the biodosimetry results have considerable uncertainty of their own, their errors are not

thought to be correlated with the errors in the survivors' dose estimates. The Statistics Department provides detailed DS02 dose estimates and other related data as well as statistical analysis for all of the biodosimetry efforts. For chromosomal aberrations, for which Genetics researchers have been accumulating results using fluorescent *in situ* hybridization (FISH), Statistics has provided initial dose-effect estimates using specialized regression models for data that are considered to be over-disperse Poisson rather than over-disperse binomially distributed,[10] due to the difference in scoring method for FISH vs. conventional Giemsa staining, and will continue to do so. (By "over-disperse," we mean that when, for example, the chromosomal aberration results are regressed on the survivors' dose estimates, one sees a scatter about the regression line that is much larger than expected from the binomial or Poisson "sampling error" due to the limited number of cells that are scored for each individual.)

Statistics also supports electron spin resonance (ESR) measurements of gamma dose in the enamel of donated teeth, which is the subject of a recent manuscript [11] by investigators in Genetics, with another manuscript in preparation, and a new international collaboration between Genetics investigators and a measurement laboratory at HIM, Germany. Support was also given to measurements by the new technique of accelerator mass spectroscopic measurements of the isotope ^{41}Ca in tooth enamel, as a measure of exposure to thermal neutrons, which were done by Genetics investigators in collaboration with HIM.[12]

Dosimetry

The Statistics Department provides ongoing support to the Dosimetry Committee's efforts to improve survivor location estimates by using mosaics of geometrically corrected pre-bombing aerial photographs of Hiroshima and Nagasaki to achieve two major goals. One is to remove local distortions in the 1945 U.S. Army maps by "rubber sheeting" them to the photographic mosaics and provide corresponding mathematical transformations from grid coordinates of the U.S. Army maps to contemporary geographical coordinates. The second is to use the photographic mosaics to directly locate, in contemporary geographical coordinates, the neighborhood drawings of survivors with shielding histories, by linking the streets and buildings depicted on the drawings to the same objects on the photographic mosaics.

The department also participates actively in efforts to evaluate potential doses that members of RERF cohorts may have received from residual radiation. This involves a number of efforts, starting with using survivor location information to make estimates of cumulative dose from fallout in known areas of fallout in both cities. Members of Statistics also participate in external collaborative research groups attempting to elucidate whether there is any evidence of undocumented fallout in areas of Hiroshima other than the known, small area in Koi-Takasu about 3 km west of the hypocenter. Recent efforts in this regard include two presentations, an interim report [13] and a book chapter (under review) on geospatial analysis of the fallout isotope ^{137}Cs measured by external investigators in Hiroshima soil samples. The department also plans collaborative work with Epidemiology to evaluate the population dose potentially associated with early entry into the cities due to gamma ray exposure from neutron-activated soils near the hypocenters.

Statistics organized and hosted an international workshop in March 2011 on ways to improve and extend DS02 organ dosimetry by using DS02's existing calculations of the energy and directional distributions of neutrons and gamma rays in shielded locations occupied by survivors. They would be combined with new computational methods and models of the human body from contemporary medical imaging technology to obtain better calculations of body self-shielding. There are a number of organs for which specific dose estimates are desirable but not currently available, such as the heart, kidney, and thymus, as well as teeth. Special meetings were held in connection with the workshop to discuss the technical issues involved in biodosimetry measurement of radiation dose using ESR on donated teeth and the need to obtain accurate DS02 calculations of dose to tooth enamel for comparison to measurements, which relates to the item on Biodosimetry above. Of particular note is that, as DS86 and DS02 include only three models of the human body for different age categories, there is a need for better modeling of the body at various ages during childhood and adolescence. Another need is for gestational age-specific doses for survivors who were exposed *in utero*.

Bioinformatics

Although members of the department are not doing research in bioinformatics as yet, Statistics recently organized and led two in-house workshops on related topics (one an overview, the second focusing on microarray and genome-wide association studies) and prepared for additional sessions on multiple testing (false discovery rate) and methods for association analysis with haplotype (phase) estimation. This workshop approach is expected to continue as needs increase for analytical methods suited to high-dimensional data, linkage to external knowledge bases, interdisciplinary integration of knowledge in a systems biology paradigm, etc.

Future Plans

The Statistics Department will continue its primary role of statistical consulting and oversight on most of the research projects conducted at RERF. This will involve design and statistical power considerations and culminate with the analysis and interpretation of the data. The department also plans to increase its role in providing statistical education to other researchers. The department will become more involved with other departments and the Information Technology Department in developing policies and procedures for data archiving and quality assessment.[14] Statistics will also continue to implement the dosimetry systems and maintain related databases. Related to the new Data Management and Documentation Committee, the department intends in the next five years to implement (within the Statistics Department) methods for effective documentation, storage, and retrieval of analytical datasets and scripts (detailed command logs of mathematical and statistical operations performed in preparing and analyzing the data). However, members of the department will also continue to conduct research on statistical problems related to issues encountered with RERF data in a number of areas.

Researchers in the Statistics Department hope to overcome computational problems in the use of Bayesian methods, especially with individual data, to: incorporate mechanistic hypotheses and family relationships (possible clustering in terms of radiation sensitivity); model missing-data mechanisms (e.g., for mail-survey data); develop flexible methods of making inference about the shape of the dose response (especially the low-dose response); and utilize more flexible and detailed error models to account for uncertainties in dose estimates.

Also, radiation risk assessment has generally been performed assuming that various causes of death are independent of each other, and this may not be true. Statistical methods for risk assessments will be examined or developed to deal with those dependencies, which would become an increasing problem at older ages when the overall force of mortality is greater.

Another focus is to further develop methods to perform analyses involving intermediate (mediating) factors, a common problem in epidemiologic and clinical datasets that is often not adequately considered. Methods for the analysis of joint radiation and other risk-factor effects involving potential mediation effects in complex models of risk prediction are expected to be worked out within the next two or three years. Plans are being made to explore methods and models used for estimating probability of radiation causation of adverse outcomes with joint risk-factor exposure and incorporating measurement uncertainties. Work will be done to consider how to translate risk estimates from complex causal models into conditional probability of causation estimates by apportioning causation between direct and mediated pathways.[15]

The basic science departments are increasingly generating data with numerous endpoints (e.g., microarrays, genome-wide scans). Such "high-dimensional data," in which the number of measured variables is often much larger than the number of samples measured (p>>n), require special methods to control for multiple testing (false discovery rates) and deal with computational issues for large numbers of covariates, many of which are correlated. Statistical and quantitative methods such as forms of regularized regression, Bayesian network analysis, etc., are rapidly evolving in this area. Some members of the department have gained expertise with some of the bioinformatics packages, and the department plans to continue developing expertise in this area, and in bioinformatics more generally, to apply new state-of-the-art methods to such data.

There is also often a need to analyze and evaluate the uncertainty (misclassification rates or standard errors) in lab results and other covariates used as independent variables in RERF studies, and to evaluate or correct for their effects on study results, particularly where there is no "gold standard" result available to validate an assay.[16] Examples of useful approaches might include the use of finite mixture models to model a set of lab results, the inclusion of random effects in a regression, or a simple analysis of the sensitivity of the results of a study to a given size of error in a key variable. Plans will be developed to improve the level of rigor in selecting or developing such methods and applying them when appropriate.

Finally, various aspects of research into dosimetry are expected to continue, including dose uncertainty and improved methods of dose estimation. Although dosimetry system DS02 provides definitive distance- and shielding-specific data on numbers of gamma rays and neutrons classified by energy and direction (fluences), recent developments of voxel phantoms have made it clear that DS02's methods of using these fluences in organ dose calculation can be improved and extended. This could involve both new Monte Carlo methods and better models of the human body emerging from medical imaging technologies, and could provide better and more extensive (e.g., to heart, fetus, and teeth) organ dose estimates. It could also provide dose estimates related to partial body exposures such as those of Nagasaki factory workers who were behind benches or other heavy equipment. The results of the recent international workshop will be used to create a scope of work for a project that can be implemented within the next three to four years.

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In the Beginning

William J. Schull, Former Vice Chairmam

As one gazes across today's Hiroshima it is nigh impossible to envisage the appearance of the city in 1947 when the ABCC (Atomic Bomb Casualty Commission) came into existence. The core of the city, which had been literally obliterated, was a patchwork of hastily constructed houses and places of business amidst which was dispersed a few renovated ferro-concrete structures that had withstood the atomic bomb's blast, such as the Nisseki Byoin and the Bank of Yamaguchi. The Heiwa dori, then known as the Hyaku meter dori, was a grassless and treeless slab of parched earth 300 feet wide, dividing the northern part of the city from the southern. Intracity transportation was a test in persistence and courage. There was the occasional trolley or bus (often charcoal burning) or bata-bata taxi or a bicycle for the intrepid. The simple act of moving from the eastern to the western portion of the city was a frustrating experience made so by the destruction or damage of so many of the city's bridges, and the devious route one had to use as a consequence. The lovely riverside parks that now line the Kyobashi-gawa were end-to-end shanties then. There was no cenotaph nor was there a suitable memorial to the thousands whose lives were snuffed in seconds on that fateful August day.

The economic situation was desperate. Food was scarce. Housing was limited. Employment opportunities were few since much of Hiroshima's heavy industry had been devoted to the war effort and in the postwar years was very slow to recover. Matters were made worse by the forceable repatriation of seven million Japanese from Korea, Manchuria, and southeast Asia in the first years following the cessation of hostilities. When those repatriates arrived in Japan they were filtered through relocation centers where they were DDTed, their health assessed for infectious disease, and then assigned to a resettlement area. It was the practice to settle them in the areas where they or their ancestors had lived prior to their migration from Japan. As a consequence of this policy, since Hiroshima and Yamaguchi prefectures have long been fertile regions for the recruitment of migrants, these two prefectures received a disproportionate number of the returnees. One of the relocation centers was on Ninoshima, and it continued to operate until the peace treaty was signed in 1951.

This was where the Commission was born and would function. It was six thousand miles from the National Academy of Science's National Research Council, its oversight organization. Despite this distance, it had to establish a research program that addressed all of society's concerns about the new threat posed by nuclear weaponry and ionizing radiation. There was no paradigm, no model that the Commission could emulate. It would sink or swim on the basis of its own perceptiveness and ingenuity. This was a challenge which under the freest of circumstances would be formidable, but the Commission was not free. It existed through the sufferance of the Occupation, on whom its material needs depended, and the cooperation of the survivors whose participation was central to the organization's very existence. The immediate issues, however, were staffing and logistics. An open-ended research program requires an open-ended capacity to recruit. But this did not exist. It was compromised by distance, nationality, and skill needs. Those barriers notwithstanding, within three years the Commission had a thousand employees. Such rapid growth brings its own problems which often involve the maintenance of a common sense of purpose and goals, but there were other complications unique to the time and location of the Commission's research activities. Nagasaki fell within the purview of the American Occupation Forces whereas Hiroshima was British Commonwealth Occupation Forces territory. In most matters this fact meant little; it was only in housing and access to some aspects of shopping where the Australian government's white-only policy was restrictive.

Construction of the buildings that now house the Foundation began with a formal Shinto groundbreaking ceremony in July 1949. Most of the work was completed by the end of 1950 when the genetics unit in the Red Cross Hospital and the clinical and administrative offices that had been in Ujina were moved to Hijiyama. Almost immediately thereafter construction was begun on the building now known as Hijiyama Hall. The latter would be occupied in late 1953. Prior to the completion of

ABCC's Ujina clinic used prior to move to new Hijiyama facilities in 1950

this building the bulk of the foreign staff lived in commandeered or newly constructed housing in Kure, Nijimura, and North Camp. The daily drive from these quarters to Hiroshima was tedious and took most of an hour. To some extent, the tedium was broken by the fishing and farming activities we saw to left and right, but after weeks even this paled. That situation would persist until 1959 when enough leasable housing became available in Hiroshima to unite all of the foreign staff. Our colleagues in Nagasaki never faced the separation that occurred in the Hiroshima area. Enough of the city had survived the bombing to provide housing for ABCC's staff.

Each of those formative years had its own bookmarks. For example, 1950 was a particularly unsettling year for the Commission and its staff for two reasons. First, the Korean war began in June of that year, and at least initially it was not clear what effect this would have on our fledgling research institution. We would learn that the needs of the forces in Korea did not impinge significantly on our logistic needs. Fuel continued to be available for our vehicles as did ample food. The second, the other signal event of the year, arose as a consequence of a disagreement between the Atomic Energy Commission and the National Research Council on the management and cost of the studies. A small committee was dispatched to Japan to assess the progress of the studies then underway and to ascertain whether the requisite quality could be maintained on a smaller budget. That committee recommended closure of the research effort. They based their decision on the absence of evidence of significant health effects (and at the time of their visit this was true), and the doubt that quality could be maintained on a sharply restricted budget. Fortunately, wiser counsel intervened and this recommendation was never implemented. However, it did have a disquieting effect upon the staff who learned that they were vulnerable to capricious decisions by "authorities" either uninterested in what was being achieved or had other agendas.

Most of us comprising the American staff in the early years served the Commission on two-year contracts that we presumed were renewable with good performance. But relatively few of the younger scientific staff actually ever renewed (myself included). This was not due to dissatisfaction with our duties in Japan, but rather our career aspirations. Those of us set on an academic career soon recognized that we were in a tenuous position insofar as recruitment to a university position was concerned. First, we were far removed from the active job market place, and were often unaware of a job opening until it had been filled. And, second, the recency of the initiation of most of the research projects and our involvement largely with design aspects meant that there was as yet no data of consequence available to publish. Given the importance of publications to the young aspirant academician, that was a serious problem. Senior staff who came to Japan on leave of absence from a university position did not share our concerns. This is of course a far cry from the situation that now prevails where lifetime employment seems to be the rule.

But life is not made up of only large decisions—there are many minor ones. The latter are more idiosyncratic generally and these affect different persons in different ways. I can only cite (by way of illustration) some of the ones that affected me. Both of my concerns will seem trivial in hindsight and perhaps they were, but some situations in life must be personally experienced to be a fair judge of the concerns of others. Since the Genetics Office was in the Hiroshima Red Cross Hospital and not with the central offices of the Commission, lunch was a daily challenge. I had two options—either to return to Ujina and the dining facility the Commission maintained there or visit the Australian forces canteen in the building housing the Fukuya Department Store. Whichever my choice, the drive shared a common peril, a swerving vehicle trying to avoid a car-swallowing pit in the road or an unsteady aged cyclist. Every new employee soon recognized that Japan is such a scenically beautiful country that a camera is a "must." While few good cameras were available on the Japanese market, the post exchange easily filled our need. There were Leicas, Contaxes, Exactas, Rolliflexes, and two new Japanese cameras, the Canon and the Nikon, that would quickly establish themselves as worthy competitors to their German counterparts.

My involvement in the studies in Japan extend over sixty years, and through that involvement I have achieved scientific maturity, or so I think. But Japan has contributed to my maturation in so many ways other than scientific stature that I shall always be beholding to Jim Neel and his invitation to be a part of this phenomenal study. Through this experience, I have learned to live with more of my senses, and yet to respect the astringent, the under-stated.

Duncan McDonald (second from right) and William J. Schull (third from left) with the officers of the Hiroshima Midwives Association in July 1951. This group collaborated in the ABCC's genetics program started in 1948.

Those of us who are native English speakers have at our disposal a language incredibly responsive to nuance, but despite this fact there is no counterpart to the Japanese word "shibui" known to me. Having said this it would be foolhardy to attempt a definition, but I can say that to me shibui implies a quiet appropriateness of a thing, a place, I suppose even an event, with regard to color, to shape, to size, to texture, and to touch. The remarks I made at RERF in May of 2010 were an imperfect attempt to express my regard for a land, a culture, and a people who have taught me so much through quiet example.

Reaching Retirement Age

Kazuo Neriishi, Consultant
Department of Clinical Studies

Upon reaching the time of my mandatory retirement at the end of December 2010, I would like to share with you some of my memories of RERF.

After completing my medical internship at Nagasaki University, I was hired by Hiroshima RERF in 1979. As I stayed in the United States for overseas study from 1981 through 1984, I actually worked at RERF for a total of 28 years. For two-and-a-half years before visiting the United States, I studied English and radiation biology every day. I remember that I read through a thick volume of radiation biology as reference for seminars held by Dr. Kelly Clifton for young researchers. For three years from 1981 through 1984, I studied at Miami University in Florida, with the aim of researching active oxygen, a subject attracting little attention in those days. Dr. Lee Frank, my supervising professor, thoroughly taught me the meaning of "scientific research." I was also greatly influenced by his sense of social responsibility. I will never forget the thrill I had upon finishing my first manuscript under his guidance.

After being assigned to the RERF Department of Clinical Studies in 1984, I decided to utilize my knowledge of active oxygen in epidemiological research. Although vitamins E and C as breast cancer inhibitors appeared to be promising topics, our lyophilized (freeze-dried) serum samples were, unfortunately, of no use. This experience gave impetus to the holding of a symposium on serum-sample preservation. Based on the recommendations expressed at the symposium, we decided on resumption of cryopreservation combined with use of lyophilization. Lyophilization, however, was later abandoned completely. A breast-cancer study was again conducted in 2002 and a series of related publications are expected in the near future. Taking over a study of benign monoclonal gammopathy (BMG) conducted by Dr. Motoko Mikami at the Research Institute for Radiation Biology and Medicine, Hiroshima University, I embarked on this new field of research (1985–1987). As Chief of the Division of Clinical Laboratories, I launched in 1986 a project of hematological and biochemical testing for all Adult Health Study (AHS) participants. At the same time, I promoted a system for including test values in reports for the study participants. An association observed between inflammation and radiation exposure in relation to active oxygen was an interesting finding.

My research focus in 1991 turned to epilation. I found that the incidence of leukemia was three times higher in individuals who experienced epilation at the time of the bombings compared to those not experiencing the disorder. Similar findings were also observed for chromosome aberrations and cataracts. My study theme was whether such differences reflected variation in radiation sensitivity or dosimetry error. Recent reports have indicated that there are variations in radiation sensitivity as suggested by such molecular biomarkers as ATM. A study of epilation using this marker would be very interesting. Because ATM suppresses development of active oxygen, it would be logical to assume that inter-individual variation of this action could be associated with radiation sensitivity.

Following the 1986 Chernobyl nuclear accident, the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) was established in 1991, resulting in my first-ever dispatch to Russia and extreme culture shock. Given the responsibility for educational activities, I ulti-

mately realized this occasion would serve as an important mission for RERF. I am pleased to learn that RERF's transition to a public-interest incorporated foundation has included a commitment to education and training activities. Ever since the JCO criticality accident in the Japanese town of Tokaimura in 1999, I have been involved in health examinations of the local residents. Due to a lack of accurate and sufficient information among both the residents and local government staff, people worry about long-term heath problems, occasionally leading to serious societal crises. In consideration of this point, I have worked on both physical and mental health management for such individual residents. I have learned through those activities that I should not be so hasty to convince those who are worried about health effects of radiation otherwise. Instead it is important to be someone with whom they can discuss problems or questions at any time. In that regard, I think my work was a positive contribution to the residents of Tokaimura.

My research focus shifted to ophthalmology starting in 2000. Based on our research, it was revealed that a dose-response relationship exists not only with subcapsular cataracts, a relationship that had already been recognized for some time, but also with cortical cataracts, and that the threshold dose for cataracts is lower than the level previously reported. I am very pleased and proud that our research was able to provide an important basis for, and contributed to, establishment of relevant radiation safety standards at the International Commission on Radiological Protection (ICRP). We also found a dose-response relationship as well as a low-dose threshold for post-operation cataracts, a marker for severe cataracts. Those findings also contributed to establishment of relevant radiation safety standards. With the establishment in 2008 of a system for collection and storage of surgically removed tissues, I am looking forward to much progress in the future in molecular biological research using such tissue samples. I believe that digitized ophthalmological images will greatly contribute to future research. In addition, I anticipate that research on whether there is an association between glaucoma and radiation will make continued progress.

I am profoundly grateful to A-bomb survivors and those scientists at university ophthalmology departments and ophthalmologist associations for their cooperation, without which our study would not have been possible. Furthermore, I realized that, when faced with challenging situations, we should not abandon our research, but instead, respond passionately to such situations in a sincere and serious manner. For example, when I found that RERF's visual field detector had not been designed to enable output of digitized data, I sent to the president of the equipment's manufacturer a letter explaining the importance of digitized data at RERF. Arrangements were then made so that software allowing output of digitized data could be developed exclusively for RERF. I was very grateful for the president's efforts.

A radiation cataractogenesis workshop was held at RERF in March 2009. Experts in the fields of epidemiology, molecular biology, and ophthalmologic medicine from the Lawrence Berkeley National Laboratory, Columbia University, Harvard University, and NASA in the United States, as well as Japanese counterparts from Kyoto University, Hiroshima University, and Nagasaki University, gathered at RERF and participated in substantive discussions. Workshop participants discussed expansion of a research protocol for storage of cataract tissues and initiation of a new protocol using the stored tissues, encouraging the advancement of comprehensive, collaborative research.

One unexpected finding from our research indicated that the difference in cataract prevalence between Hiroshima and Nagasaki may be due to the difference in quantity of ultraviolet-ray exposure. The latitudes of the two cities differ by only 1.6 degrees. Our research indicated, however, that ultraviolet rays might also be an important risk factor for potentially explaining the inter-city differences between Hiroshima and Nagasaki in terms of skin cancer and other disorders (Minamoto A, Neriishi K, Nakashima E. UV radiation may explain intercity difference for cataract in A-bomb survivors. *J Photochem Photobiol B* 2011; 103:105–10). Amid the concerns over the biological impact of depletion of the ozone layer, we may have contributed data relevant to that environmental issue and how strong physical effects of radiation are. I hope this research will progress further in the future.

I would like to conclude my article by mentioning a letter from an AHS participant. The participant wrote in the letter: "I was recently diagnosed as having acute myelogenous leukemia with a poor prognosis. As I will be unable to visit RERF any more to undergo health examinations, I would like to enclose a copy of my examination results to serve as reference materials for your future research." A detailed medical history was also enclosed. That person was apparently determined to fully live what remained of life, calmly contemplating mortality. I continue to ask myself, "how can I fully respond to the person's wishes?" I would like to close by expressing my sincere appreciation to all of you for the kind support you extended to me over so many years.

Research Protocols Approved in November 2010–April 2011

RP 1-11 Study of Radiation-induced Circulatory Diseases Using Animal Models

Takahashi N, Niwa Y, Ohishi W, Hayashi T, Murakami H, Hsu WL, Kokubo T, Inaba T, Kusunoki Y

The Life Span Study (LSS) data indicate radiation-associated risk for hypertensive heart disease and stroke, and the Adult Health Study (AHS) data suggest radiation-associated risk for hypertension. We hypothesize that radiation may result in higher risk for circulatory diseases (CD). However, there are a limited number of animal model studies that have examined the relationship between radiation and CD at doses under 4 Gy, although some papers report that various biomarkers are affected by radiation. In this study, we propose the use of spontaneous hypertension rat-stroke prone (SHRSP) rats as rat CD models. Radiation doses from a brief single exposure will be given to the rats at 4, 2, and 1 Gy, with non-exposed (0 Gy) rats used as controls. We will evaluate acceleration of the development of hypertension in the SHRSP rats after radiation exposure. Moreover, we will measure candidate serum markers that have shown radiation dose effects based on previous AHS studies. In addition to serum markers, we will also measure 23 biomarkers in plasma samples by immunoassay. The priority of each plasma marker will be determined on the basis of previous results from AHS studies, and we plan to examine the effects of radiation exposure in morphological types in autopsy tissues by collaborating with the Institute for Environmental Sciences. This study will provide mechanistic information on the association between radiation exposure and development of CD.

RP 2-11 Study of Arteriosclerosis in the Adult Health Study Population (Part 2. Analysis of the Cytokine Network Regulating Differentiation of Mesenchymal Stem Cells in Artery)

Takahashi I, Ohishi W, Hayashi T, Cologne JB, Takahashi T, Kusunoki Y, Ozasa K, Kihara Y, Matsumoto M, Fujiwara S

Reports regarding therapeutic irradiation of the human head and animal experiments, as well as reports involving mortality and incidence of arteriosclerotic diseases among A-bomb survivors, have suggested that high-dose radiation induces arteriosclerosis, but the mechanism of such induction is unclear. It is difficult to explain the entire picture of the complex clinical condition of arteriosclerosis with the conventional hypothesis that arteriosclerosis is an inflammatory disease. Tissue damage is probably of primary importance in relatively high-dose-radiation-induced arteriosclerotic changes. In this study, therefore, we will consider arteriosclerosis based on the "inflammation-response-to-injury" hypothesis. We hypothesize that diseases related to "artery-bone metabolism-immunity" are abnormalities in differentiation and proliferation of arterial mesenchymal tissue. Thus, we also will measure several multi-functional cytokines in 2,100 Adult Health Study (AHS) subjects (including those exposed at young ages). That cross-sectional study is designed to test our hypothesis that "abnormalities in the cytokine network initiated by tissue damage at the time of radiation exposure induce abnormalities in mesenchymal tissues." We will obtain measurements of arteriosclerotic markers (augmentation index [AI]; brachial-ankle pulse wave velocity [baPWV]; ankle-brachial index [ABI]; intima-media thickness [IMT]; calcification of aortic arch and/or abdominal artery) and cytokines (pentraxin-3 [PTX-3]; osteopontin [OPN]; osteoprotegerin [OPG]; receptor activator of nuclear factor [NF]-κB ligand [RANKL]; vascular endothelial growth factor-A [VEGF-A]; high mobility group box-1 [HMGB-1]; apolipoprotein-J [Apo-J], also called clusterin; interleukin-17 [IL-17]), which will be measured once during the four years (two cycles) starting in 2010 that constitute our study period. We also will measure reactive oxygen species (ROS), which act as proliferation signals for mesenchymal stem cells. We will then examine if the "cytokine network" functions to either moderate or mediate the radiation effect upon atherosclerotic cardiovascular outcomes.

RP 3-11 Radiation Exposure in Children and *In Utero* Survivors of the Atomic Bombing of Hiroshima and Nagasaki and Late-life Neurocognitive Function

Yamada M, Hida A, Akahoshi M, Kasagi F, Abbott RD, Khattree R, Ohshita T, Miyachi T, Matsumoto M, Tsujino A, Mimori Y, Krull KR, Fujiwara S

We will examine late-life neurocognitive function among the Adult Health Study subjects who were exposed *in utero* or aged <12 years at the time of the atomic bombing of Hiroshima and Nagasaki. Objectives are (1) to examine associations between radiation exposure and neurocognitive function as assessed by neuropsychological examination, (2) to investigate the effects of sex, age, attained education, lifestyle, and comorbidity on neurocognitive function as risk factors or modifiers of radiation effects, and (3) to collect baseline data on cognitive function for the investigation of longitudinal progression in cognitive decline with advancing age and the occurrence of dementia. The Cognitive Abilities Screening Instrument (CASI) and the Childhood Cancer Survivors Study (CCSS)-Neurocognitive Questionnaire (NCQ) will be used as instruments for neuropsychological assessment.

Recent Publications

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