



Message from the Chairman

Toshiteru Okubo

On this occasion of the publication of our Annual Report FY2013, I would like to express my sincere gratitude, on behalf of the Radiation Effects Research Foundation (RERF), for the unwavering cooperation of so many people, starting with the A-bomb survivors. Their support allowed us to continue smoothly developing our research operations in FY2013.

The RERF Future Plans stipulate organizational objectives by setting out a long-term vision of striving to be an ever more comprehensive global center of excellence (COE). To make progress toward this vision, we are working hard to put into practice a more flexible research system in the foreseeable future. Specifically, we are implementing a project-oriented research system in which research activities are conducted by joint teams that transcend departmental barriers, based on the core RERF mission of conducting long-term follow-up studies of A-bomb survivors and their children.

To fulfill our long-term aim of becoming an enhanced COE, we must tackle other challenges as well, such as improvement of administrative structure, human resource management, and budgetary matters. Furthermore, we firmly believe that a key factor in enabling research scientists to fulfill their duties is the continued creation of a better work environment, in terms of both physical infrastructure and “soft” facets, in our research and support departments. RERF therefore needs to promptly establish an appropriate research management system that will allow scientists to effectively generate high-quality research results.

The ongoing personnel reduction plan mandated by the Japanese national government continues to ask RERF to reduce the number of its employees by approximately five persons each year. RERF also faces the aging of mid-level employees and attrition through retirement. Under such circumstances, we have found it very difficult to maintain our prior level of operations using only incremental efforts such as standardization of workloads. To address this challenge, RERF is now working on improving its overall organizational structure.

The RERF Biosample Center was established in April 2013. This has allowed us to take a significant step toward the centralized management of biosample storage and utilization, which has been one of the key elements in translating RERF’s Future Plans into reality. We have also nearly completed a series of projects that began in 2009 to review dosimetry data for individuals, with the corrected dosimetry data expected to be widely accepted and put into use.

Among events in FY2013, RERF was presented with a letter of appreciation by the Minister of Health, Labour and Welfare for our participation in support activities related to the health management survey of the victims of the Fukushima Daiichi nuclear power plant accident. This recognition would not have been possible without the many years of understanding and support provided by the A-bomb survivors for our research activities, regarding which we are truly grateful. We will further discuss how we can continue to cooperate in such important efforts by maximizing the know-how we have accumulated from our long-term health effects studies of A-bomb survivors.

I close by kindly requesting everyone’s continued understanding and support of RERF research activities.



Message from the Vice Chairman and Executive Director

Roy E. Shore

Epidemiologic data on mortality and cancer incidence among A-bomb survivors (Life Span Study [LSS]) and their children (F_1 generation studies) have long been a primary basis for national and international estimates of the risks of cancer and other diseases from exposure to ionizing radiation. The unique importance of the LSS study stems from the combination of its large size, wide range of exposure levels, inclusion of all ages at exposure, long high-quality follow-up, and comprehensive data on mortality and cancer incidence. However, the LSS is only one facet of RERF's research activities. Clinical examinations and biosamples in the Adult Health Study (AHS, a subsample of the LSS) and the clinical study of the children of A-bomb survivors provide more detailed information on health conditions of interest, especially radiation-related noncancer conditions, and opportunities to study the pathogenesis of those conditions in relation to radiation exposure. Our basic-science groups utilize the biosamples to further address the nature and extent of genetic and molecular changes associated with the health risks. Hence, the RERF studies provide a unique and important window into both epidemiological and biological aspects of radiation risk.

To highlight a few of the more important papers and findings during the year:

- ◆ Little information has been available on soft tissue sarcoma induction by radiation at low-to-moderate doses. LSS data showed an approximately linear dose response among A-bomb survivors, with exposure of 1 Gy doubling the risk of soft-tissue sarcoma development (Samartzis et al., *J Bone Joint Surg Am* 2013; 95:222–9).
- ◆ Two studies showed that immune-related biomarkers were associated with the risk of various cancers: hepatocellular carcinoma (HCC) was associated with serum levels of IL-6, but the HCC radiation risk was not modified by IL-6 levels (Ohishi et al., *Int J Cancer* 2014; 134:154–63). The diffuse-type of gastric cancer was associated with radiation for the common *IL-10* gene haplotype (Hayashi et al., *Radiat Res* 2013; 180:60–9).
- ◆ Another study asked the question of whether obesity, which is a risk factor for colon cancer, modifies the risk of radiation-related colon cancer. There was no evidence that obesity modifies the radiation risk (Semmens et al., *Cancer Caus Cont* 2013; 24:27–37).
- ◆ Issues of low-dose radiation have become increasingly important due to both the 2011 nuclear accident in Fukushima and the many medical, environmental, and occupational sources of low-dose exposure. We held an international low-dose workshop to address issues in estimating low-dose risks, especially as they apply to the atomic bomb survivor studies. To mention just a few of the numerous topics touched upon in the workshop: It is important to look at different cancer sites separately, since the molecular pathways of cancer induction vary across sites. Strategic use of biosamples can help address gaps in our knowledge. The LSS is a valuable source of information on individual tumor sites, but pooled analyses of low-dose data from multiple studies are probably needed to more precisely define low-dose risks for many tumor sites. Confounding by disease risk factors could have more impact on low-dose studies than those with a large dose range, because the magnitude of the variations in susceptibility may approach or even exceed the size of the dose effect in the low-dose study. Likewise, dose uncertainties will be especially important to consider for low-dose analyses.
- ◆ Regarding radiation and cardiovascular disease (CVD), we published a paper on radiation damage to the kidneys and showed that the kidney dysfunction impacts cardiovascular risk factors (Sera et al., *Radiat Res* 2013; 179(1):46–52). We also published a summary of our workshop on radiation and CVD

that was held the prior year (Takahashi et al., *J Radiol Prot* 2013; 33(4):869–80). A collaborative paper examined whether a healthy survivor effect had distorted the radiation dose-response curve for CVD effects, but found no evidence of such distortion (Schöllnberger et al., *Radiat Protect Dosim* 2014, in press).

- ◆ Past A-bomb survivor reports suggested that radiation exposure may be related to noncancer respiratory disease mortality. We therefore undertook a study to investigate whether the apparent association arose from confounding by other risk factors or from misdiagnosis of other diseases as respiratory. We found that a substantial part of the association was due to death-certificate misdiagnoses of cancer as being nonmalignant respiratory disease (Pham et al., *Radiat Res* 2013; 180:539–45).
- ◆ Another paper showed that radiation dose was associated with a decrease in body mass index (BMI) and in the proportion of lean body mass (Tatsukawa et al., *Int J Obes* 2013; 37:1123–8).
- ◆ A screening study investigated whether radiation was associated with glaucoma. It found that glaucoma with elevated eye pressure was not related to radiation dose, but that normal tension glaucoma may be related. However, methodologic uncertainties substantially limited the conclusions that could be drawn (Kiuchi et al., *Radiat Res* 2013; 180:422–30).
- ◆ Certain blood biomarkers associated with influenza vaccine antigens have been found to differ by radiation dose and age. Preliminary results indicate that radiation dose significantly affected GM-CSF and IL-4 responses to vaccination. Analysis has not yet been completed on the association of radiation dose with antibody titers.
- ◆ It was found that intracellular reactive oxygen species levels, notably levels in suppressor T cells, increased with age and radiation dose. This indicates that exposure to radiation is associated with chronic oxidative stress.
- ◆ There was no indication of risk from either paternal or maternal radiation exposure for the adult-onset multifactorial diseases of hypercholesterolemia, hypertension, diabetes, angina, myocardial infarction, or stroke in the clinical examination of about 12,000 offspring of A-bomb survivors (Tatsukawa et al., *J Radiol Prot* 2013; 33:281–93). However, the offspring will need to be followed up for several more decades to older ages to obtain definitive evidence.
- ◆ A study employed 2.1 million probes per mouse genome using comparative genomic hybridization (CGH) technology to detect *de novo* genomic deletions and duplications in the offspring that result from parental radiation exposure. No evidence was found of heritable radiation effects on the frequency of genomic deletions or duplications, but possible signatures of radiation effects at the breakpoint sequences of several mutations were identified in the exposed group.
- ◆ Work on creating accurate maps and correcting location (using geographic information system [GIS] technology) and structural shielding data of LSS study subjects has been completed. A substantially revised model of elevation and terrain shielding and its application to LSS subjects also was completed. Preliminary analyses suggest these changes will make little difference in the risk estimates, but will reduce uncertainties and increase confidence in the dose calculations.
- ◆ Reported exposure to fallout rain was obtained from early Atomic Bomb Casualty Commission (ABCC) questionnaires. Because of public concerns, especially after the Fukushima nuclear power plant accident, the fallout data have been analyzed in relation to subsequent cancer and noncancer mortality and cancer incidence. No clear association was seen between reported exposure and the health outcomes. A paper summarizing the results is currently under internal review.

The RERF research provides benefits to A-bomb survivors in terms of early disease detection and informs both the survivors and the world at large about the risks from radiation exposure. Such knowledge is important because of the many uses of radiation in today's world. We want to thank our sponsors, the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, who strongly support our research on the health effects of atomic radiation. We especially want to thank the many A-bomb survivors and their children who have faithfully participated for many years in clinical studies that provide invaluable knowledge which benefits all humankind.