

FY2017 Plans of Activities

Introduction

Epidemiologic data on mortality and cancer incidence among A-bomb survivors (the Life Span Study [LSS], the *in utero* study) and their children (the F₁ 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 the collection of biosamples in the Adult Health Study (AHS, a subsample of the LSS) and the clinical, epidemiological and genetic studies of the children of A-bomb survivors provide more detailed information on health conditions of interest, including radiation-related non-cancer conditions, and the pathogenesis of those conditions in relation to radiation exposure. We are also staging heritable mutations. Our basic science groups in collaboration with the clinical studies and epidemiology departments utilize the biosamples to further address the nature and extent of genetic (both heritable and somatic) effects, and molecular changes associated with the health risks. These three components within the RERF research program provide a unique and important integrative approach into epidemiological, clinical, biological, and mechanistic aspects of human radiation risk. Such integrated opportunities are unique to RERF and make essential that the best science possible is conducted.

I. Major Activity Plans

1. Research Projects Examining A-Bomb Survivors Health

1) Radiation and Cancer Risks

An increased incidence of cancer is recognized as the primary risk. A summary of some of the activities that focus on providing information related to risks and characterization of potential mechanisms involved in radiation related cancer is provided below:

- *Updated cancer incidence:* A series of papers of cancer incidence risk of radiation for individual sites in the LSS during 1958–2009 will be published in 2017 and beyond in collaboration with US National Cancer Institute. Individual organ sites or organ systems expected to be submitted for internal review in 2017 include: upper digestive system, lower digestive system, hepato-biliary-pancreatic, and uterine. Other systems to follow include prostate, urinary, CNS, second cancers, and other cancers.
- *Site-specific cancer studies with histological reviews in the LSS cohort:* Active studies will be continued in collaboration with the US National Cancer Institute. Data analyses of radiation risks will be conducted and papers will be submitted for bone and soft tissue tumors, malignant lymphoma, and breast cancer. Histological reviews by pathologists will be continued for uterine (corpus) cancer. A pilot study for genomic analysis of thyroid cancer will be conducted in collaboration with US National Cancer Institute and RIKEN.
- *Radiation risk at low dose levels:* Current efforts on cancer incidence risk analysis at low-dose levels will be developed, in collaborations between the Epidemiology and Statistics Departments, in preparation for mortality risk analysis in the LSS. The analysis will include non-cancer diseases, which are thought to be more influenced by lifestyle and socioeconomic status that were possibly associated with the geospatial distribution of the

survivors. Dose errors as well as the potential impact of exposure to residual radiation and medical radiation will also be considered.

- A collaboration between the Clinical Studies and Statistics Departments to investigate the contribution of chronic inflammation, insulin resistance, and liver fibrosis, indexed by CRP, TNF- α , IL-6, adiponectin, leptin, and type 4 collagen, to HCC risk and to assess their possible mediation effects, along with HBV/HCV, in the etiology of radiation-related HCC will continue.
- A collaborative program with Nagasaki University and Kyoto University to determine mutations in serially collected blood samples from individuals developing AML or MDS using genomic analysis will begin.

2) Radiation and Risks of Circulatory Disease

While studies of cancer risks has been the main focus of studies at RERF it has been more recently recognized that significant risks for non-cancer effects may also exist. Risks of cardiovascular disease have been of particular interest and a few of the ongoing studies are described below:

A multidisciplinary approach developed through the Non-cancer Research Cluster will be applied in studying CVD because epidemiological, clinical and basic studies are all underway at RERF. Discussions regarding areas of work to be engaged in by researchers from each discipline have been as follows;

- Epidemiology: Non-cancer disease mortality, etc.
- Clinical Studies: Disease incidence/ prevalence, risk factors (hypertension, lipid profile, inflammatory markers, etc.), clinical testing including atherosclerotic indices, etc.
- Basic studies: immunologic, immune-genome, basic research on stem/progenitor cells, hypertension genes, animal experiment, etc.
- Statistics: Risk modeling, modeling of intermediate variables, multidimensional analyses, etc.

The research questions to be worked out include;

- At what doses is there a radiation effect?
- Shape of dose-response curve? Is there a dose threshold?
- Impact of age at irradiation?
- Impact of joint irradiation of the kidney or other organs?
- Modifiers of risk – gender, age at exposure, cardiovascular risk factors, related diseases (CKD, DM etc.), genetic susceptibility factors?
- What possible mechanisms need more investigation?

The following investigations will be conducted led by the Department of Clinical Studies.

- Complete collecting data cross-sectionally to investigate the relationship between radiation dose and heart function or manifestations among the AHS participants using echocardiography and pertinent preclinical biomarkers.
- Initiate analyses of a CVD incidence study using consistent criteria over the study period since AHS had started, especially for ischemic heart disease (IHD) and stroke in the AHS.

- Develop analysis plan to examine relationships between radiation dose and blood biomarkers such as inflammatory cytokines (IL-6, TNF- α , etc), adipocytokines (adiponectin, etc) and IGF-1, and ensuing CVD risk.
- Continue collaboration with Statistics Department to review the association between radiation and CKD and the joint role of CKD in the radiation-CVD association based on diagnoses and detailed categorizations of CKD using estimated glomerular filtration rate (e-GFR) and micro-albuminuria among Hiroshima and Nagasaki AHS subjects. Complete analyses and prepare a manuscript.
- Continue to examine the dose response for the development of diabetes in Hiroshima and Nagasaki and to evaluate whether the radiation dose response for diabetes is modified by city and age at the timing of A-bomb.
- Complete analyses regarding radiation exposure and atrial fibrillation (AF), which is one of the arrhythmias and prepare a manuscript.

3) Other Noncancer Risks:

- *Cataract:* Radiation effects on posterior sub-capsular opacity have been well documented among A-bomb survivors and other exposed population. With regard to radiation effects on cortical/ nuclear opacities, however, evidence appears to be insufficient and study results are inconsistent. Therefore, we have developed new ophthalmological study to obtain lens images by 3 devices; slit-lamp, retro-illumination camera, Scheimpflug camera with standardized method to evaluate the grade of posterior sub-capsular, cortical, and nuclear opacities.
- *Late life cognition:* Regarding late-life neurocognitive function using Neurocognitive Questionnaire (NCQ) survey instrument among subjects exposed in utero and at ages <13 years at the time of the bombings, a factor analysis for non-exposed subjects will begin in a collaborative analysis between Clinical Studies and Statistics Departments. We will then, analyze radiation effects on neurocognitive-deficit symptoms based on NCQ and/or cognitive function based on Cognitive Abilities Screening Instrument (CASI).

4) Activities to Enhance Ongoing and Future Analysis:

Establishing a strong infrastructure is essential to conduct high quality studies. Some of the most significant activities are described below:

- *Mortality surveillance:* Mortality follow-up for all cohorts will continue and the data will be completed through 2013. Archiving early-time materials will be continued.
- *Hiroshima and Nagasaki tumor/tissue registries:* Case collection on population-based cancer registries will be completed through 2014 in both Hiroshima and Nagasaki. Cross-check of cancer incidence information with RERF database will be biennially updated in 2018 on the LSS, *in utero*, and F₁ cohorts. Annual reports of cancer incidence in the local populations will also be released. The data will regularly be reported to the Monitoring of Cancer Incidence in Japan (MCIJ) and cooperative studies with the National Cancer Center of Japan are also being conducted. Analyses of the prefectural data of Hiroshima and Nagasaki will be conducted. RERF will continue to make efforts to adapt to the new Japanese National Cancer Registry System.
- *Pathology studies:* The indexing of specimens of formalin-fixed paraffin-embedded tissues within a new database is continuing. We will continue to make efforts to preserve and utilize pathological materials from the A-bomb survivors in collaboration with

community hospitals in Hiroshima and Nagasaki. These activities will be performed in cooperation with the RERF Biosample Center.

- *Biosample Center:*
- Continue an inventory of archive biosamples stored in deep freezers in Nagasaki.
- Complete specific and detailed regulations on sample usage, including the limit of amount used, and a sample use request form, by incorporating the opinions of experts.
- Create a manual on quality control: review methods of quality control (including storage temperatures and effects of thawing and refreezing) as necessary to improve the quality control of samples and examine their stability.
- Work on the establishment of laboratory information management system (LIMS).
- Continue an effort to have understanding and acceptance on the use of biosample for research from A-bomb survivors and local community
- Establish internal/external advisory committees on the operation of Biosample Center and protocols for distribution of samples

5) Mechanistic Studies to Provide a Better Understanding of Risks:

Crucial to the understanding of risks and facilitate our focus on the health of A-Bomb Survivors are focused mechanistic studies.

- The efficiency of *EML4-ALK* fusion gene to generate PTC will be evaluated in a conditional transgenic mouse model. Radiation dose effects on the time required for tumor formation will also be evaluated to investigate the biological significance of rearranged ALK gene in radiation-related PTC.
- More than 300 SNPs at genes related to immune function, inflammation, and DNA repair have been recently genotyped in the Immunogenome cohort. We will now perform gene-set and pathway analyses to study interaction between genes and radiation on radiation-associated colon cancer development. One paper is expected.
- We will design a nested case-control study using Japonica array developed for analyzing gene polymorphisms in the Japanese population, that are potentially involved in the development of radiation-associated breast cancer.
- One paper describing telomere length and its change with age in old populations of US and Japan is expected in 2017. Another paper on the development of a predictive scoring system based on radiation and age is also expected.
- One manuscript on association of ILC3 commitment with DNA integrity in HPCs of A-bomb survivors will be submitted, and one manuscript on classification of human circulating HPCs at a single cell level will also be prepared. Another paper on radiation-associated changes in the number and function of DC populations is expected in 2017.
- Data analysis for TCR diversity evaluated by deep sequencing will be completed, a manuscript on longitudinal TCR diversity change will be submitted, and a future *TCR* deep sequencing study in A-bomb survivors will be planned.
- A longitudinal study of changes in T-cell subsets in 1,000 AHS participants will continue to test the hypothesis that declining T-cell immunity may relate to elevated risks of inflammatory diseases, such as myocardial and cerebral infarctions, liver diseases, and stroke, in A-bomb survivors.

- As previous studies at RERF in a rat model system demonstrated a high sensitivity between radiation and CVD. Studies will be expanded in which we will examine rats irradiated with low dose and low dose rate irradiation to estimate the dose and dose rate effectiveness factor (DDREF) for CVD. Since this system provides the opportunity to determine potential mechanisms underlying radiation effects on CVD, we will conduct studies to identify biomarkers associated with the development of CVD.

2. Research Projects on the Health of A-Bomb Survivors Children (F1)

An important question for understanding of risks following the atomic bombings, and exposure to radiation in general, is whether there are transgenerational effects that could result in an increased cancer or non-cancer risk in the children of survivors (F1). Studies of these F1 offspring include clinical studies, epidemiological studies, and basic science.

1) Clinical

- *Clinical exams:* In 2016 we have almost completed the second round examination of the longitudinal F1 offspring clinical study (FOCS) cohort that begun in November 2010 on a four-year cycle, and established a participation rate of 78.5% (10,377 subjects).
- *Analysis:* Using data available from earlier clinical examines we have conducted preliminary tabulation of the prevalence and incidence of individual multifactorial disease outcomes among participants during the first three years of the four-year second round, in preparation for future analysis plan

2) Epidemiology

- *F₁ cohort study:* A cancer incidence paper should be written but it is difficult to estimate the migration rates of F₁ cohort members out of cancer registry areas. As cancer incidence information diagnosed in all Japan since 2016 will be available in the National Cancer Registry, the information might become a major source for cancer incidence analysis in F₁ cohort. Radiation effects on the F₁ generation will be investigated in an integrated program project with other departments developed in the Genetic Research Cluster.

3) Mechanistic Studies to Investigate Potential Transgenerational Effects

- We will evaluate radiation-induced mutations and analyze parental origins of *de novo* base substitutions in F1 mice born before and after irradiation to male germ cells by whole genome sequencing.

3. Research to Elucidate Individual Radiation Doses and the Effects from A-bombs

Fundamental to all of the RERF studies is well defined dosimetry. This is an ongoing process as new information is obtained and new techniques become available.

- We will use individual-data analytic methods to characterize sources and types of uncertainties in atomic-bomb radiation dosimetry and their impact (covariate error) on risk estimates and develop ways to correct for this, including simulations and use of biodosimetric information. We are working with several groups of external collaborators and expect continued production of statistical papers and useful results for practical application at RERF,
- We will continue the evaluation of the potential impact on the LSS of doses from external exposure to residual radiation,
- We will begin to develop ways to apply geospatial methods to RERF data to take full

advantage of existing two-dimensional information on survivor locations at the time of the bombings, testing assumptions such as circular symmetry in the dosimetry and spatial homogeneity of background rates over large areas of the cities. This involves modern methods such as hierarchical Bayesian or empirical Bayesian methods. RERF data present challenges for spatial analysis, as they are strongly influenced by direct radiation dose from the bombs and other covariates, the effects of which must be estimated from the same data as part of a simultaneous analysis. Specific projects may ultimately include spatial analyses of acute epilation, chromosomal aberrations, and cancer incidence,

- We will continue to investigate the possible doses that survivors may have received from indirect sources, i.e., residual radioactivity, in a collaboration with RERF Epidemiology and possibly external investigators, as we have done for DOE-sponsored workshops in 2012 and 2014 and in support of two recent Epidemiology papers on exposure to rain shortly after the bombings.
- We will publish 2 papers describing results from comparison of ESR data with DS02 doses and cytogenetic-estimated doses from the same donors.

4. Project to Release of Research Results and to Collaborate with Other Scientific Organizations

- *Continuing collaborations:* Long term collaborations are listed below and these are expected to continue in 2017:
 - a. Partnership with Kurume University
 - b. Collaborations with the US National Cancer Institute
 - c. Collaborations with the US National Institute of Allergy and Infectious Diseases
 - d. Collaborations with Outside Investigators:
 - 45 Japanese Institutions
 - 22 North American Institutions
 - 12 European Institutions
 - 6 Asian Institutions
 - Nuclear Emergency Workers Study (NEWS): 10 Japanese Institutions

5. Training Programs for Domestic and Overseas Specialists

RERF will hold a training seminar for non-epidemiologist radiation researchers to learn the basics of epidemiological research and increase understanding of radiation health risks. In addition, RERF will train persons capable of working in the fields of radiation protection, radiation emergency medical care, and radiobiological research.

Activity plans for this fiscal year:

- i) RERF will hold an epidemiological training seminar for radiation biologists in Japan again this year for enhanced understanding of results from epidemiology research on A-bomb survivors.
- ii) RERF will accept overseas research trainees to support the activities of such organizations as the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE), the Nagasaki Association for Hibakusha's Medical Care (NASHIM), and the Japan International Cooperation Agency (JICA).
- iii) Besides the above activities, RERF will accept students from domestic and overseas schools/universities for facility tours, and will provide training sessions on the foundation's research activities.

- iv) RERF will continue to review directions as to its training activities and publicly invite overseas trainees in the International Exchange Research Program for this fiscal year also.

6. Public Information Programs

Activity plans for this fiscal year

i) RERF Open House event

RERF will hold its 23rd and 21st Open House events at the Hiroshima and Nagasaki RERF Laboratories, respectively. The event features various programs, including exhibitions, and lectures, and is scheduled to be held in Hiroshima and Nagasaki on August 5–6 and August 8–9, respectively. Additional marketing funding will be allocated to discern whether it positively affects visitor numbers.

ii) 70th RERF commemorative event

RERF is planning to hold a public event commemorating its 70th anniversary in June of FY2017, to provide the general public with an opportunity to enhance their understanding of the foundation's research and to learn more about radiation's health effects.

Dates: Hiroshima (June 19); Nagasaki (next fiscal year)

iii) Permanent exhibits

Our permanent exhibits at the Hiroshima and Nagasaki Laboratories introduce the history of ABCC-RERF, the organization's study/research activities, its domestic and overseas collaborative activities, and contributions RERF has made to society. The walkway in Unit DA is being upgraded little by little, and of particular note, the Historical Panel information update will be on full display in FY2017 with both English and Japanese languages used to convey ABCC/RERF historical information.

iv) Updating of public relations materials

RERF will update its various public relations materials, including *Update* and the Japanese version of *A Brief Update*.

v) New RERF website

In FY2017, RERF will announce to the public its new website after complete redesign. This new website will be much more attractive to the average user and will invite him or her to explore our online information more easily than was possible previously. Also, with the new design, the user can easily access the website on mobile and other devices. With the comprehensive change to the website, some of the content will naturally change as well, possibly leading to the use of more video and so on. RERF will continue to post information, with a focus on video format, on its Facebook page.

vi) School Visit Program

This program was first established in FY2016 in an attempt to teach young students the reality of radiation health effects. With the stable of teachers firmly established, a concerted effort to market this event will go into full effect in FY2017.

vii) Other public relations activities

- RERF will actively promote the foundation's important papers to the domestic and overseas media via press releases and press conferences.
- RERF will try to speak before the Foreign Correspondents Club of Japan in Tokyo, in a continuation from our first effort, which took place in February FY2016.

- RERF will once again organize annual forums for media representatives in Hiroshima and Nagasaki.
- RERF will develop a proactive public relations system collaborating with all its professional and general staff in a unified manner.
- RERF will seek an efficient approach with respect to its facility tours and train more personnel to handle the tours in English for overseas visitors.

II. Activities necessary for the above projects

1. Review of job performance evaluation system and its implementation

The RERF's job performance evaluation system for the general employees was initially enacted in 1977 and then fully revised to the current system in 2011. Although six years have passed since the current system was established, the system has met many challenges and there are some employees dissatisfied with or disappointed in the system.

One of the reasons for RERF having difficulty in properly utilizing the present job performance evaluation system is that we have a wide variety of occupations (such as clinical laboratory technician, radiologist, nurse, clerk, secretary, interpreter/translator, and computer engineer), despite a relatively small number of 160 general employees. On top of this, we have some departments where those to evaluate and to be evaluated have been fixed for more than ten years, since frequent personnel transfers have been made difficult due to the ongoing personnel reduction plan. Also, at the Hiroshima Laboratory, due to the structure of the building, some departments have their staff members working in separate small rooms, and this has made it hard for some evaluators to properly observe job performance.

RERF has held regular training sessions and explanatory meetings for the evaluators, and the regulations regarding the job performance evaluation system were partially revised in FY2014. However, the system has its shortcomings.

For the aforementioned reasons, RERF will review the current job performance evaluation system and consider overhauling it drastically and fundamentally in order to establish a system that helps the general employees to maintain high motivation based on a fair, impartial, and satisfying evaluation.

2. Multi-year personnel plan for Secretariat

Management-level (section chief) personnel in the Secretariat average 55 years in age, and the majority are reaching mandatory retirement age within the next 2-4 years. This situation is quite serious in that capable successors, in some but not all sections, will not be easy to put in place. With this in mind, a complete review of all staff within the Secretariat is being and will be further undertaken so that a long-term plan for each section can be implemented. This plan will identify future staff for each section, especially at the section chief and assistant section chief level, and will likely encompass a merging of certain sections as one method of dealing with the dearth of management-level personnel.

3. Converting temporary employees to permanent staff members

RERF has three general methods of hiring new staff: hiring of new graduates, hiring of mid-career persons from outside, and converting RERF's current temporary employees to permanent employees.

Although each of these methods has benefits, the benefits of converting the temporary employees to regular employees are that, based on their work at RERF, we can judge their job

performance, ethical standards and personality, and relations with other staff members. Another great benefit of converting is that the temporary employees can be work-ready, with minimal training necessary.

For the time being, RERF would like to make full use of the benefits of converting the temporary employees to permanent employees and make recruiting plans based on this approach.

4. Planning to motivate staff to aspire to management-level positions

Employee training, conducted since FY2008 with the primary aim of raising staff awareness, has proven successful to some extent. However, the questionnaire survey for employees in supervisory positions conducted last year found that many assistant section chiefs are somewhat reluctant to be promoted to the position of section chief and above and that some section chiefs would like to relinquish their present posts. Most employees in supervisory positions are due for mandatory age retirement within five years. Plans to motivate the staff to aspire to senior positions must be developed as soon as possible to improve the present situation.

5. Possible continuation of internal audit process

An internal audit system was newly introduced in FY2016. The report of the internal audit for the first fiscal year, FY2016, will be submitted to the RERF Auditors by the internal auditor during the first quarter of FY2017. At the regular meeting of the Board of Councilors in 2017, the directors will report the progress made in improvement of the internal audit system, and the Auditors will make their audit report. Whether to continue the internal audit in FY2017 will be discussed.

6. Facility upgrades

(1)Upgrades to Hiroshima Laboratory

- 1) Installation of the robotic biorepository was completed in October 2015. Since it is predicted that existing generators, No. 1 - No. 4, will not be able to produce sufficient backup power, an additional generator, No. 5, will be installed at an estimated cost of 50 million yen.
- 2) Wall painting will be carried out at an estimated cost of 4 million yen to beautify the buildings' passageways and rooms.

(2)Upgrades to Nagasaki Laboratory

No upgrades to the Nagasaki Laboratory are scheduled.