Report of Major Activities

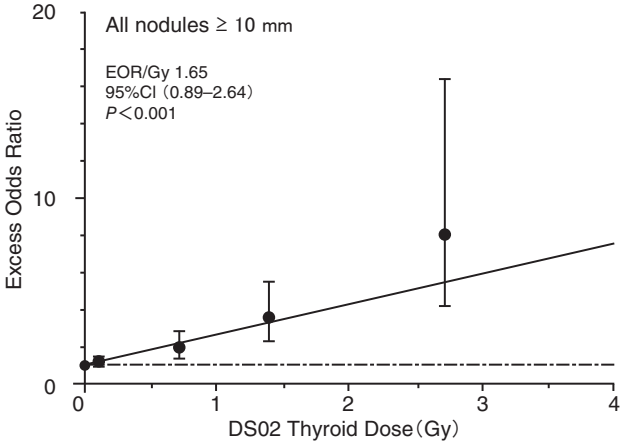
1. Research projects on A-bomb survivors' health

(1) Radiation research based on the Life Span Study (LSS), *in utero*, and Adult Health Study (AHS) cohorts

Radiation and cancer risks

Cancer risks have continued to be the most prominent adverse health effects associated with radiation exposure among A-bomb survivors for more than 60 years after the bombings. A variety of studies related to radiation and cancer risks are in various stages of progress, and several highlights are mentioned below:

- *Updated cancer incidence:* The LSS provides the leading comprehensive assessment of lifetime risk from radiation exposure. To that end, with collaboration by the U.S. National Cancer Institute, extensive work is underway on an 11-year updated analysis of the radiation risk for cancer incidence to 64 years after the atomic bombings. The new analyses are based on the updated version of the DS02 dosimetry that corrects map misalignments and individual locations at the time of the bombings and significantly improves the estimation of terrain shielding. The new reports will include detailed analyses of total solid cancers and a number of individual tumor sites focusing on the shape of the dose-response curves. The analyses have an increased emphasis on radiation risks from childhood and adolescent exposures since that subpopulation is now coming into the ages at which cancers are expressed with much greater frequency. The increasingly robust cancer dataset and the public health interest due to the Fukushima accident also provide a strong rationale for focusing on cancer risks from low-dose exposures. Variations in cancer susceptibility due to lifestyle and other factors motivate analyses to look at the degree to which those factors modify radiation risks. Preliminary results were presented at an international radiation meeting and publications are expected within the next year.
- *Low-dose workshop:* Much public interest focuses on low-dose exposures because of Fukushima and medical exposures (e.g., CT exams). A report based on the RERF international workshop on low-dose radiation risk has been accepted for publication. Among the topics considered are low-dose risk estimation and uncertainties; the impact of other risk factors on low-dose studies; generalizing risk estimates to other populations; incorporation of genetic and molecular susceptibility information; examination of various cancer sites separately, since the molecular pathways of cancer induction vary across sites; and strategic use of biosamples to address gaps in mechanistic knowledge.
- *In utero cohort study:* This is the only extant study of disease experience in adulthood following prenatal radiation exposure, a topic of importance since *in utero* exposures have occurred in many settings and the prenatal period may be a time of high radiation sensitivity. Analyses of cancer and noncancer mortality risks for 1950–2008 are being completed. Solid cancer mortality risk was elevated in relation to radiation dose, with a suggestively higher risk among females. An increased risk in relation to low-birth weight was observed for total non-cancer disease mortality after high doses, but the interpretation of this association is unclear.
- *Breast cancer:* Female breast cancer shows one of the highest radiogenic relative risks of any cancer site. The molecular subtypes having to do with cellular estrogen and progesterone receptors (ER/PR) and human epidermal growth factor receptor 2 (Her2) status are currently of particular interest, since the limited data available from other studies suggest that the ER/PR negative subtype may be more highly associated with radiation exposure, particularly exposure at younger ages. A histological review of over 1,300 cases was undertaken, along with immunohistological staining of breast cancer specimens, to determine subtypes according to ER/PR and Her2 status. This review is nearly completed and analyses will be conducted.
- *Breast cancer risk factors:* The possibility also is being examined that breast cancer radiation effects are mediated through alterations in endogenous sex hormone levels. An analysis suggests that part of the radiation risk may be mediated through alterations in estradiol levels. A paper on this has been submitted for publication. We are also participating in a consortium analysis of premenopausal breast cancer and selected lifestyle factors headed by the Institute of Cancer Research, UK.
- *Thyroid neoplasms:* The thyroid gland is one of the most radiosensitive organs, and information on lifetime thyroid cancer risk is important for, e.g., Chernobyl and Fukushima risk estimation. Thyroid examinations in the AHS showed that both thyroid cancer and other thyroid nodules had approximately linear associations with radiation dose (Imaizumi et al., *JAMA Internal Medicine* 2015; 175:228–36), and risk is continuing even 60 years after exposure (Figure 1).



EOR/Gy:Estimated excess odds ratio for those 5 years old at exposure

(Imaizumi et al., *JAMA Intern Med* 2015; 175:228–36)

Figure 1. Thyroid nodules in younger atomic bomb survivors (age at exposure < 10 years, N = 2668, 2007–2011). Dose-response for thyroid nodules ≥ 10mm in diameter among A-bomb survivors exposed in childhood. (Points and vertical bars represent the best estimates and 95% confidence bounds of risk for various dose subgroups.)

- *Studies of radiation and liver cancer:* Hepatocellular carcinoma (HCC) was associated with serum levels of interleukin-6 (IL-6), but the HCC radiation risk was not modified by IL-6 levels (Ohishi et al., *Int J Cancer* 2014; 134:154–63). Departments of Clinical Studies and Statistics are collaborating to investigate the pathogenesis of radiation-associated HCC by analyzing markers of chronic inflammation, insulin resistance, and liver fibrosis, and by examining the degree to which the association of radiation and HCC may be mediated by hepatitis-B or hepatitis-C viral infections. These factors may help explain why liver cancer radiation risk seems to be greater in the LSS than in western populations.

Site-specific LSS cancer studies with histological review

Several pathology studies are currently ongoing in collaboration with the U.S. National Cancer Institute, including:

- *Uterine cancer:* Previous analyses of uterine cancer were not able to distinguish reliably between uterine corpus (endometrial) and cervix cancer, two sites that reflect divergent etiologies, because many uterus cancer notifications several decades in the past did not distinguish between the two. Since a preliminary analysis of more recent data suggested that corpus but not cervical cancer might be related to radiation exposure, a histopathological evaluation is being conducted for corpus cancer to more accurately determine the magnitude of radiation risk.
- *Malignant lymphoma*: The tumor incidence data have suggested an association of malignant lymphoma with radiation for men but not for women. However, the histologic subtypes and risk factors that may be associated with this are unknown, and therefore a detailed study incorporating histological review of over 450 cases is being analyzed.

Radiation and circulatory disease risks

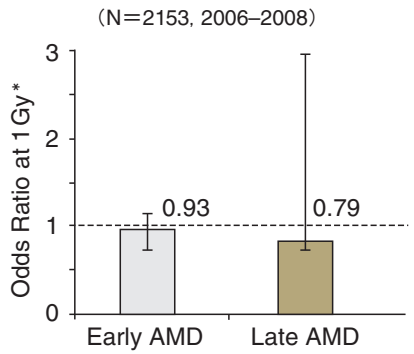
Because of recent findings in the LSS regarding the association of radiation with circulatory diseases, the RERF Cardiovascular Disease (CVD) Working Group has spurred the development of several studies to learn more about the potential biological mechanisms by which low-to-moderate doses of radiation may confer risk for cardiovascular and cerebrovascular diseases.

- *Improved assessment of chronic kidney disease (CKD) and CVD risk:* Radiation effects upon organs other than the heart, such as chronic kidney dysfunction, may be implicated in CVD risk. We previously reported that eGFR (estimated glomerular filtration rate), one measure of kidney dysfunction, was associated with both radiation and CVD risk factors, and we are now examining both eGFR and microalbuminuria jointly to better characterize the association between radiation and CKD and the role of CKD in radiation-associated CVD.
- *Roles of biological and physiological risk factors in radiation-CVD risk:* A number of measures relevant to CVD risk from radiation are being studied in the AHS to assess the roles of various biological pathways and pre-clinical indicators of cardiovascular disease. Examples include: markers of chronic inflammation, insulin resistance or adipocytokines, such as tumor necrosis factor (TNF)-α, IL-6, monocyte chemotactic protein (MCP)-1, leptin, resistin, adiponectin and insulin-like growth factor (IGF)-1; physiological measurements reflecting atherosis (fatty deposits) or arterial stiffness; and visceral fat accumulation and fatty liver disease.
- *Echocardiographic screening:* Because associations of radiation exposure with mortality from heart failure, hypertensive heart disease, and valvular heart disease have been reported in the LSS, we aim to confirm and evaluate these disease risks in the AHS and develop mechanistic insights. To obtain early indicators of these types of disease, we have begun a study using echocardiography and disease-related preclinical biomarkers.
- *Heart arrhythmias:* Little is known about heart arrhythmias in relation to low-to-moderate radiation doses. A study was begun on radiation dose and atrial fibrillation, a common arrhythmia which may increase risk for heart failure and stroke. A paper on the prognostic significance of premature ventricular contractions also was submitted for publication.
- *Are radiation-CVD mortality results confounded by the healthy survivor effect?:* We collaborated with researchers from the Helmholtz Institute (Munich, Germany) and found no evidence that a healthy survivor effect had distorted the radiation dose-response curve for CVD effects (Schöllnberger et al., *Radiat Protect Dosim* 2015).
- *Experimental circulatory disease:* To help confirm the A-bomb studies suggesting that circulatory diseases may be caused by radiation at moderate doses, an experimental study is ongoing to validate the epidemiologic and clinical findings using a strain of rats that is susceptible to stroke. The study is examining doses to 0.25 Gy for early stroke symptoms and mortality, along with biochemical measurements and pathologic analyses. Radiation related changes in blood pressure are being examined in a related strain that is susceptible to hypertension.

Radiation and health outcomes other than cancer or circulatory disease

A-bomb radiation exposure has been related to a variety of additional health outcomes.

- *Radiation, diabetes and dyslipidemia:* Little research is available regarding whether radiation exposure is associated with diabetes mellitus risk. A new RP will examine the dose response for measures related to blood glucose and lipids and the development of diabetes mellitus. Those measures will also be related to risk of CVD and chronic kidney disease.
- *Radiation and cognitive deficits:* A paper was submitted on the effects of demographic factors and radiation on the age trend of cognitive function between 1992 and 2011 among subjects with radiation exposure at 13 or more years of age. Data also are being collected on cognitive function among those who were exposed in childhood or *in utero*.
- *Vision limitation–macular degeneration:* A paper was submitted on radiation effects upon age-related macular degeneration in the AHS. No statistically significant



*Adjusted for city, gender, age, and smoking habit

(Sakata et al., submitted)

Figure 2. A-bomb radiation exposure and the prevalence of age-related macular degeneration (AMD). Study of A-bomb radiation exposure and the frequency of macular degeneration of the retina. (An odds ratio of 1.0 represents the normal frequency without radiation exposure. "Late AMD" represents diagnoses of "neovascular AMD" or "geographic atrophy.")

association with radiation was found (Figure 2).

Activities to provide for future high-quality studies of cancer and other health endpoints

- *Hiroshima and Nagasaki tumor/tissue registries:* Case collection by notifications and death certificates is complete through 2012 in both Hiroshima and Nagasaki prefectures. Case abstraction from medical records has been completed through 2011 in Hiroshima and 2013 in Nagasaki, and abstraction of the more recent cases is underway.
- *Pathology studies:* A database that indexes RERF specimens of formalin-fixed paraffin-embedded tissues is being developed for future specimen utilization. A system to preserve surgically resected materials from the A-bomb survivors is being organized with an increasing number of community hospitals in Hiroshima and Nagasaki. These activities are performed in cooperation with the RERF Biosample Center.
- *Adult Health Study (AHS) clinical examinations:* The AHS is conducting its 28th round of biennial clinical examinations of atomic bomb survivors. About 98% of the participants provide informed consent for RERF to use their blood and urine specimens for future non-genomic research studies and 91% for genomic studies as well.
- *F_1 clinical examinations:* The second round of clinical assessment of F_1 offspring of A-bomb survivors is essentially complete. About 83% of those enrolled in the first round have participated the second time as well, an excellent retention rate. Over 10,000 subjects were examined.
- *Medical radiation exposures:* Reported medical diagnostic and therapeutic radiation exposures from the recent mail survey are being analyzed to determine if that source of radiation exposure confounds the A-bomb dose-response association or affects the risk estimates. Preliminary analyses suggest there is little confounding, but further analysis is being undertaken.
- *Research data documentation:* It is now required to submit documented analytic datasets to the Department of Information Technology before study publication, so that RERF can be assured of having a record of the data on which its reports are based. Consideration is also being given to ways to improve the searchability for legacy and recent data variables to enhance integration and data access for researchers.
- *Biosample Center*: Planning and preparations have been conducted for the Biosample Center to become fully operational in FY2015. Specifically, this included 1) preparations for the installation of an automated bio-repository system (–80°C BioStore II), 2) compiling of descriptions and information on biosamples that are to be preserved, 3) preparation for development of the associated database system, and 4) planning of a system for the use of biological sample materials.

(2) Research on biological mechanisms related to health effects from radiation among A-bomb survivors

Understanding the biological mechanisms underlying radiation effects on health can help sharpen assessments of, for example, low-dose risks and can provide clues regarding disease prevention and treatment. Several studies of biological mechanisms of radiation health effects have already been summarized above in the sections on various types of disease. Additional research is described below.

- *Radiation and epigenetic cancer mechanisms:* We are conducting pilot studies to evaluate epigenetic alterations (i.e., modification of genetic functions by means other than through changes in the DNA) based on the hypothesis that radiation might cause epigenetic changes in DNA transcription or DNA methylation that lead to increased risks of selected diseases. A pilot study has begun to develop appropriate bioinformatics methodology for transcriptomic gene expression based on RNA sequencing, in collaboration with Hiroshima University and the Fred Hutchinson Cancer Research Center. The technique will be used to address whether variations in gene expression are associated with radiation exposure.
- *Cytogenetic studies following fetal irradiation:* We found that chromosome translocations were induced in rat mammary epithelial cells following fetal irradiation, whereas they were not induced in fetal lymphocytes (Nakano et al., Radiat Res 2014; 181(2):172–6). This parallels the tissue-dependent induction of malignancies among the *in utero*-exposed A-bomb survivors. We also observed that translocation frequencies in mouse thyroid cells irradiated as fetuses varied with fetal stage at the time of irradiation. This suggests that the time of anchoring of stem cells to their niches may be related to tissue specific radio-sensitivity as a function of the stage of fetal development.
- *Metabolomics and circulatory diseases:* To develop greater mechanistic understanding of radiation impacts on blood metabolites and how they affect circulatory disease, a pilot study is performing a metabolome-wide analysis of the blood of stroke-prone rats. The pilot study will seek to detect reliable metabolomic patterns that differentiate irradiated and unirradiated rats, with the intent that a subsequent larger study can investigate metabolomic

patterns/pathways conducive to radiation-associated hypertension and stroke.

- *Radiation and cancer mechanisms:* Ongoing cancer studies aim to clarify mechanistic relationships between radiation exposure and cancer development among A-bomb survivors. Studies of early molecular events in the development of cancers in the LSS cohort are being conducted, particularly studies of gene rearrangements in thyroid cancer (Figure 3), mutator phenotypes in colorectal cancer, and lung cancer mutations in radiation-exposed survivors.

Past RERF immunology studies indicated that both immune cell counts and immune function were compromised by radiation. Some current studies:

- *Radiation and immune responsiveness to vaccination:* Certain blood biomarkers (e.g., GM-CSF and IL-4) associated with influenza vaccine antigens have been found to differ across radiation and age groups. Analyses are underway on the association of radiation dose with influenza vaccination antibody titers and their functional implications.
- *Mechanisms of radiation immune effects:* A microassay system to evaluate functions of human circulating hematopoietic progenitor cells (HPCs) was established to study long-lasting radiation effects on the immune system. A study using blood samples from in-house volunteers indicated a linkage between dendritic-cell and T-cell differentiation potentials in HPCs (Kyoizumi et al., *J Immunol* 2014; 192:5749–60). Dendritic cells and T cells trigger and mount immune defenses, respectively.
- *T-cell profiles and obesity:* A reduction in newly produced ("naïve") T cells was significantly associated with increased body mass index and inflammation (Figure 4), suggesting that obesity with enhanced inflammation may be involved in the aging of the human T-cell immune system (Yoshida et al., *PLoS One* 2014; 9:e91985d).
- *Telomeres:* Shortened DNA telomeres, which are an indication of cellular aging, may also confer risk for cancer and other chronic diseases. A cross-sectional study showed that leukocyte telomere lengths in A-bomb survivors exposed when young to >700 mGy were significantly shortened compared with those exposed to <5 mGy.

2. Research projects on the health of A-bomb survivors' children (F_1)

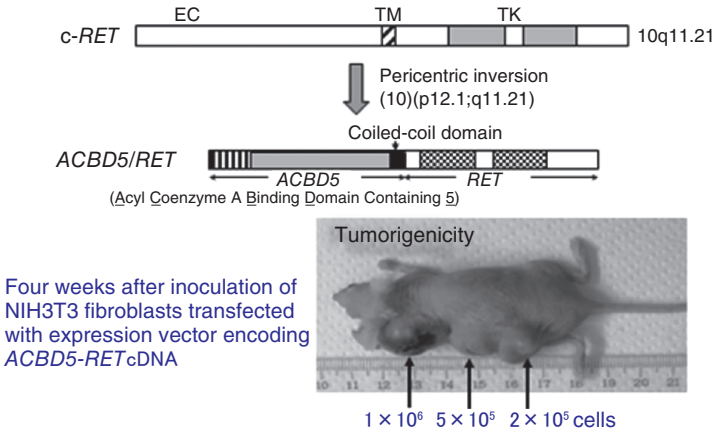
(1) F_1 mortality study and F_1 clinical study

- *F_1 epidemiologic cohort study:* Long-term studies of the F_1 cohort address the key issue of possible heritable effects of radiation exposure as assessed by the frequencies of adult-onset diseases. They provide unique data regarding this issue, as this is the only extant cohort with such data. A 14-year update through 2009 of cancer and noncancer mortality risks in the epidemiologic cohort of 77,000 F_1 offspring of A-bomb survivors has been submitted for RERF pre-publication review. No significant increase in cancer or noncancer disease mortality was seen in relation to individual paternal or maternal gonadal doses, but the offspring are still relatively young and longer follow-up is required.

(2) Research on biological mechanisms related to the health of A-bomb survivors' children

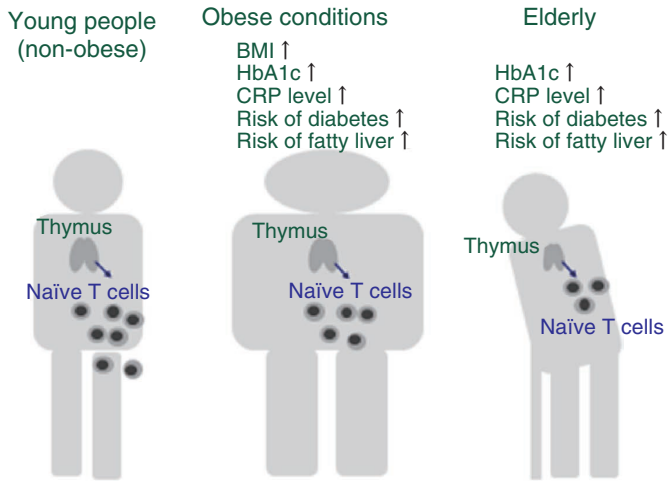
Trans-generational genetic effects are being studied using modern technologies with biosamples from the offspring of A-bomb survivors or of experimental animals.

- *Recombinant mouse model:* Alternate ways to document persisting mutational effects are useful. We submitted a paper regarding the generation and characterization of a newly established recombinant mouse model (HPRT-dup-GFP mice) for detecting radiation-induced somatic and germ cell mutations *in vivo*. Work is underway to produce a GFP construct that reflects a mutation associated with radiation detriment (involving non-homologous end joining) and is applicable to a variety of genes, so that mutated tumor oncogenes or tumor-



Hamatani et al., *Oncol Rep* 2014; 32:1809–14

Figure 3. A novel *RET* rearrangement (*ACBD5/RET*) in thyroid cancer from an A-bomb survivor exposed to high-dose radiation (1.8 Gy). Evidence that a specific alteration in the *RET* gene was involved in the development of thyroid cancer in a high-dose A-bomb survivor: the gene alteration was also found to be the cause of cancer in a mouse.



Yoshida et al., *PLoS ONE* 2014; 9:e91985

Figure 4. Obesity indicators and reduced thymic T-cell production levels in aging A-bomb survivors. Production of protective naïve T cells by the thymus is reduced with both aging and obesity (BMI, indicator of obesity; HbA1c, indicator of blood plasma glucose concentration; CRP, indicator of vascular inflammation).

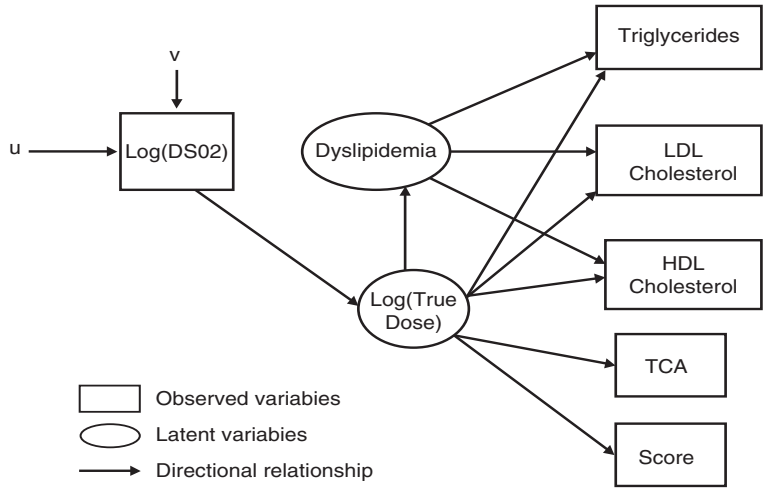
suppressor genes can be studied in relation to radiation exposure. This may provide new insights about the genetic effects of radiation at low doses.

- *Experimental estimation of the radiation-induced mutation rate:* This study employed 2.1 million probes per mouse genome using CGH (comparative genomic hybridization) technology to study *de novo* genomic deletions and duplications in offspring after parental radiation exposure. No evidence was found of heritable radiation effects upon the frequency of such deletions or duplications, but possible signatures of radiation effects at the breakpoint sequences of several mutations were identified in the exposed group. In another study, no risk of heritable mutations was found based on 2D-DNA electrophoresis analyses of F_1 rats derived from irradiated immature oocytes (Asakawa et al., *Radiat Res* 2014; 182:430–4).
- *Genetic study of the offspring of A-bomb survivors using high-density microarray CGH analysis:* CGH analyses of DNA from mother-father-child(ren) sets with a microarray of 1.4 million probes have been completed on DNA samples from 688 family members to detect genomic DNA deletions or duplications associated with parental radiation exposure. We are currently conducting PCR-based molecular validation of the candidate mutations found. Results using multiple bioinformatics approaches will be compared.
- *Detection of single nucleotide variants (SNVs) and small insertions/deletions (indels):* Pilot studies of DNA *de novo* base substitutions (SNVs/indels) are being conducted using next generation sequencing because previous techniques could not detect such small, but potentially significant, mutations. The studies involve whole genome sequencing of DNA from irradiated human cell lines or from F_1 mice born to an irradiated female mouse.

3. Research to elucidate individual radiation doses and the effects from A-bombs

(1) Investigation of conditions required for dose estimates including survivor location, shielding effects and organ dosimetry

- *A-bomb physical dosimetry:* The work on creating accurate maps and correcting location and structural shielding data of LSS study subjects has been completed. We reviewed the original records and confirmed the location at the time of the bombings, pinpointing the locations on geographically corrected maps for the LSS and *in utero* cohorts and the F_1 cohort parents. A substantially revised model of elevation and terrain shielding was applied to these cohorts. Preliminary analyses suggest these changes will make little difference in the average risk estimates, but will reduce uncertainties and increase our confidence in the dose calculations.
- *Relative biological effectiveness (RBE) of neutrons:* The impact of neutron doses from the bombs has continued to be of interest for risk assessment. A publication provided a clarification of the correct methodology to calculate the variable (dose-dependent) type of relative biological effectiveness (RBE) factor for neutrons in estimating A-bomb risks when based on experimental data from radiation biology, and also showed that the estimates of A-bomb neutron RBE based directly on RERF data were intrinsically uncertain (Cullings et al., *Radiat Res* 2014; 182:587–98).
- *Fallout exposures:* The RERF data are not highly specific regarding exposures to radioactive fallout (in "black rain"). Nevertheless, because of intense local interest in the fallout issue, especially after the Fukushima accident, a number of analyses to determine if black rain accounts for observed health effects have been undertaken and published (Sakata et al., *Radiat Res* 2014; 182:599–606).



Tekwe et al., *Statist Med* 2014, 33:4469–4481

Figure 5. Statistical method to incorporate biodosimetry with DS02 dose estimation in relation to a multivariable index of dyslipidemia. Dose uncertainty reduction using biodosimetric data in relation to dyslipidemia: Using physical dosimetry (DS02), chromosome aberrations (TCA), and a radiation acute-symptom score (Score), one can improve the estimation of the unobservable "true" doses, and relate it to a latent-variable construct such as "dyslipidemia" (based on measures of triglycerides and subtypes of cholesterol). The combination of multiple variables with appropriate statistical techniques provides better estimates of associations of radiation and disease.

In comparing the risks for noncancer mortality, and for both the mortality and incidence of solid cancers and leukemia, between the groups reporting "black rain" exposure or no exposure, no clear association with reported fallout exposure was seen (see figure at bottom on page 22). An analysis of fallout rain exposure and reported acute symptoms (e.g., hair loss) also has been conducted to address concerns about an alleged association, and a paper is submitted for publication.

- *Dose uncertainties:* In the area of statistical modeling of dose uncertainties and the use of biodosimetric data to reduce uncertainties (Figure 5), we have extensive collaborations with three different external groups of statistical investigators. This year one paper was published (Tekwe et al., *Stat Med* 2014; 33:4469–81) and two more have been submitted for publication.
- *Organ dosimetry:* The currently applied model to estimate A-bomb organ doses from air doses according to age and gender was developed in the early 1980s, but more sophisticated methods and computerized human "phantoms" are now available. We are organizing an expert working group to develop new computational phantoms for use with DS02 to calculate improved organ doses and fetal doses.

(2) Research on statistical methodology needed for risk analyses of atomic bomb radiation

- *Low-dose risk uncertainties:* The Statistics Department is developing methodology to examine risk uncertainties in dose-response data, particularly at low doses. A new method provides more flexibility and less reliance on prior assumptions than the conventional methods, and provides more realistic estimates of uncertainty at low doses.
- *Intermediate risk factors:* Work is underway to develop methods for the analysis of intermediate risk factors with stratified (counter-matched) nested case-control and case-subcohort sampling designs. Those methods are needed for several RERF studies but they have not been developed in the statistical literature, and they may have wider applicability.
- *Imputation of missing data:* The Statistics Department is examining multiple imputation and other approaches to model missing data (incomplete or missing for a fraction of the LSS cohort) in estimating the joint effects of radiation and smoking on lung cancer risk (Figure 6), with application to other risk factors and other cancer sites as well. A methodological paper was published on a new imputation method to address the issue with our complex data set (Furukawa et al., *Stat Methods Med Res* 2014).

4. Project to release research results and to collaborate with other scientific organizations

Efforts have been made to develop a number of research collaborations and other joint projects with both domestic and international organizations and researchers working in the field of radiation effects.

(1) Research project on radiation-related immunity and aging under contract with the U.S. National Institute of Allergy and Infectious Diseases (NIAID)

To define the effects of ionizing radiation on

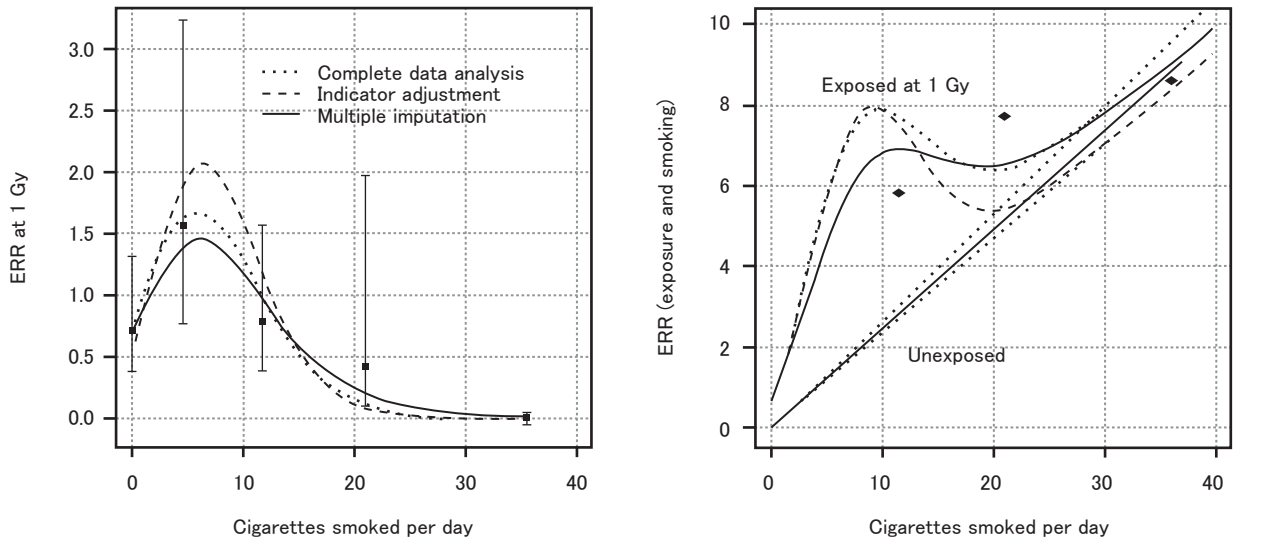
immunological function and aging and gain insights about underlying mechanisms, RERF is now in the sixth year of a collaborative study with four Japanese and five U.S. institutions under a research contract with NIAID. This study will provide a variety of information on fundamental biologic processes and evidence on the impact of radiation on immune-related health effects.

(2) Other ongoing collaborative research projects

- Collaboration with the U.S. National Cancer Institute
  Several site-specific cancer incidence studies based on histopathological review are now active (female breast, lymphoid tissue, uterus, soft tissue/bone). The collaboration has led to numerous publications over the years, and research activities and mutual feedback will continue. They are also extensively collaborating with us in the new analyses of solid cancer incidence.
- Collaborative research programs in the areas of radiation epidemiology and statistics to increase opportunities for the foundation to recruit researchers in epidemiology and biostatistics to work at RERF. Studies are ongoing with Kurume University investigators.

(3) Facilitation of collaborative studies

We currently have collaborations with 20 research institutions in North America, 19 research institutions in Europe and 5 research institutions in Asia. We also have collaborations with investigators at 37 research institutions in Japan. All the research departments at RERF are engaged in such studies. We continue to develop collaborative studies, and new ones are anticipated during FY2015 and beyond as opportunities, ideas or needs develop.



(Furukawa et al., *Stat Methods Med Res* 2014)

Figure 6. An improved statistical method to handle missing smoking data in estimating smoking and radiation risks for lung cancer
Left panel: The radiation-associated excess relative risk (ERR) of lung cancer at 1 Gy (compared to unexposed persons of the same smoking habits). Right panel: The joint excess relative risk of smoking and 1 Gy of radiation (compared to unexposed never-smokers). Estimations are shown for only persons with complete data, or for all persons with an indicator variable for missing data, or for multiple imputation for missing data. Risks are plotted as a function of number of cigarettes smoked per day. In the right panel, the straight lines show the ERR for smoking intensity but no radiation exposure, and the curved lines for those additionally exposed at 1 Gy. The points (with 95% CI in the left panel) are based on a combination of radiation and smoking-intensity categories. All estimates are gender-averaged risks at age 70 when smoking started at age 20. Multiple imputation tends to provide better estimation of the amounts of radiation risk when there are missing data.