Report of Major Activities

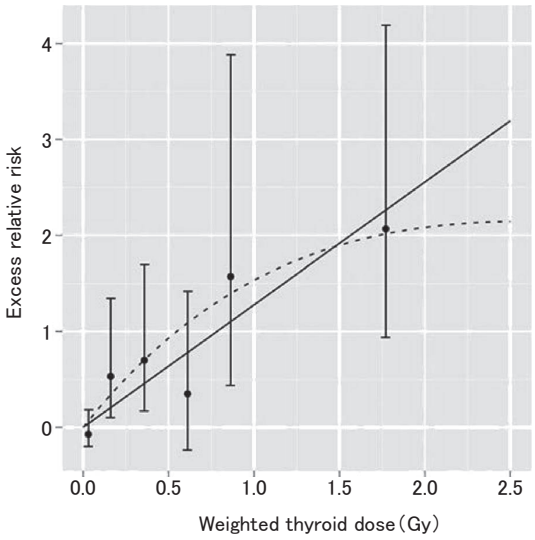
1. Research projects on A-bomb survivors' health

(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:

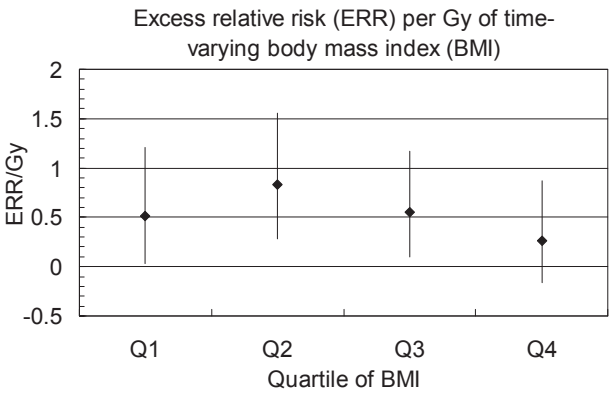
- Updated cancer incidence: Extensive work is underway on a comprehensive analysis to update for an additional 11 years the radiation risk for cancer incidence, in collaboration with the U.S. National Cancer Institute (NCI). The new analyses will have increased emphasis on radiation risks from childhood 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 nuclear power plant 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.
- Low-dose workshop: A workshop on "The evaluation of the effects of low-dose radiation exposure in the atomic bomb survivors" was held in December 2013, to discuss issues in low-dose research and approaches for investigating low-dose radiation risks in the RERF cohorts. The talks and discussions by RERF scientists and experts from the U.S., Europe, and Japan covered many aspects of low-dose studies. Some specific topics were: estimation of low-dose risk uncertainties, dose uncertainties and confounding by other sources of radiation exposure, generalizing risk estimates to other populations, the application of radiation biological studies to epidemiologic risk estimation, the impact of other risk factors in low-dose studies, effect-modification of radiation risks, incorporation of genetic and molecular susceptibility information, and considerations in the interpretation of low-dose studies. Publication of a report on the workshop is planned.
- *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. An analysis of cancer and noncancer mortality risks for 1950–2008 has been completed and a paper is undergoing internal review before submitting for publication. Solid cancer risk was elevated in relation to radiation dose, with a suggestively higher risk among females. An increased risk in relation to low-birth weight with *in utero* exposure to high-dose radiation was observed for total noncancer disease mortality, but the interpretation of this association is unclear.



(Furukawa et al., *Int J Cancer* 2013; 132(5):1222–6)

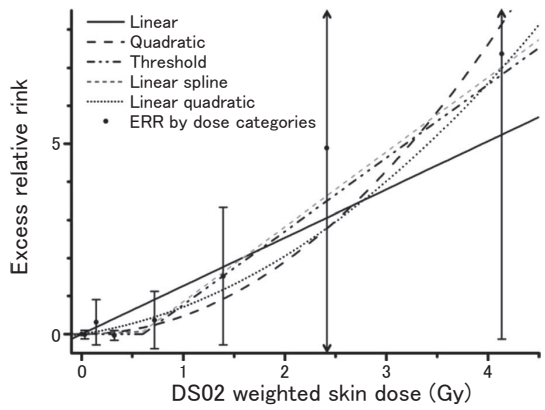
Figure 1. Excess relative risk for thyroid cancer by thyroid dose. Fitted dose-response functions for thyroid cancer incidence in the LSS cohort. The solid line is the fitted linear ERR dose response, and the dashed curve is the fitted ERR based on a linear-exponential dose-response model. The line and points are all gender-averaged estimates at age 60 after exposure at age 10.

- Breast cancer: The possibility is being explored that breast cancer effects are mediated through radiation-associated alterations in endogenous sex-hormone levels. Analyses have been conducted and a paper has been drafted.
- Breast cancer subtypes: A breast cancer pathology study also is underway to determine whether radiation risk varies by histological subtypes or molecular ER/PR/Her2 subtypes. The molecular subtypes 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.
- Thyroid cancer: A publication on thyroid cancer showed a continuing high radiation risk among those exposed as children, but little risk following adult exposure (Furukawa et al., *Int J Cancer* 2013; 132:1222–6). The excess risk was evident at doses above about 100–200 mGy and has persisted for more than 50 years (Figure 1). A new statistical method is being applied to better evaluate the uncertainties in risk at low doses. A detailed analysis in relation to radiation and lifestyle factors is being conducted in collaboration with the U.S. NCI.
- Colon cancer: This study asked the question of whether obesity, which is a risk factor for colon cancer, modifies the risk of radiation-related colon cancer. No radiation effect modification was found (Figure 2) (Semmens et al., *Cancer Caus Cont* 2013; 24:27–37).
- Radiation, immune genotype, and gastric cancer: For the diffuse-type of gastric cancer the association with radiation depends on the major *IL-10* genetic haplotype, with no radiation-cancer association for those with the homozygous minor gene haplotype (Hayashi et al., *Radiat Res* 2013; 180:60–9).



(Semmens et al., *Cancer Causes Control* 2013; 24:27–37)

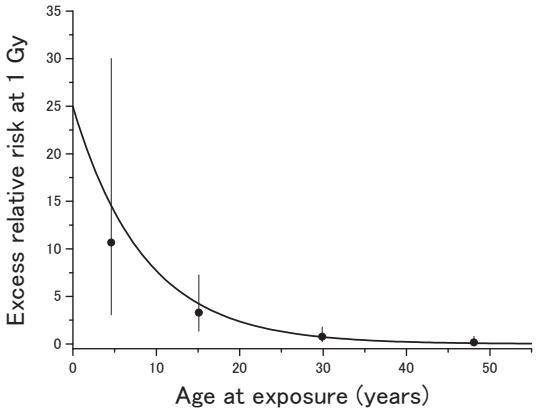
Figure 2. Radiation risk of colon cancer (excess relative risk at 1 Gy) by the body mass index (BMI) of obesity. The risk of colon cancer incidence significantly increased independently due to both radiation exposure and increased BMI, but the degree of radiation risk was not significantly modified by BMI. Time-varying, longitudinal BMI estimates were obtained from responses to repeated questionnaires (mail surveys) and adjusted for age. BMI quartile cut-points differed by gender. The ERR/Gy was adjusted for city, sex, not-in-city, and sex-specific attained age and age at exposure. The vertical bars indicate 95% confidence intervals.



(Sugiyama et al., *Radiat Res* in press)

Figure 3. Basal cell skin cancer incidence by radiation dose. Dose-response curves for various excess relative models. The models included sex, period at diagnosis, and log age 70 as the background parameters, and age at the time of bombing as an effect modifier.

- Radiation, inflammation, and cancer risk: Higher serum levels of IL-6 were associated with increased hepatocellular carcinoma (HCC) risk, independently of hepatitis virus, lifestyle, and radiation. The interaction of obesity with IL-6 levels in relation to HCC risk was significant, but that of radiation with IL-6 levels was not observed (Ohishi et al., *Int J Cancer* 2014; 134(1):154–63). A manuscript on the mediating role of chronic inflammation in promoting radiation-related cancer risk also has been submitted to an international journal.
- Site-specific LSS cancer studies with histological review: Several pathology studies are currently ongoing in collaboration with the U.S. NCI. A paper on skin cancer has been submitted with findings that basal cell and squamous cell skin cancer incidence were dose-dependent, but with an apparent dose threshold of about 0.6 Gy (Figure 3). Risk was most apparent for those exposed at young ages (Figure 4). No association with radiation was seen for malignant melanoma.
- 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.



(Sugiyama et al., *Radiat Res* in press)

Figure 4. Basal cell skin cancer excess relative risk at 1 Gy by age at exposure. Excess relative risk at 1 Gy by age at exposure based on a linear model with a threshold at 0.63 Gy.

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.

- CVD Workshop report: A CVD Workshop report was published (Takahashi et al., *J Radiol Prot* 2013; 33(4):869–80). It explored aspects of our current knowledge and issues about radiogenic CVD effects and suggested additional directions for research. The directions included, for example, further analyses of heart disease subtypes; examination of radiation-risk modification by other CVD risk factors; and indications that microvascular damage, altered metabolism, hypertension, and damage of other organs (e.g., kidney) may impact CVD risk after low-dose total-body irradiation.
- Chronic kidney disease (CKD): Radiation effects upon organs other than the heart, such as CKD, may be independently implicated in CVD risk. Chronic kidney disease, assessed by eGFR (estimated glomerular

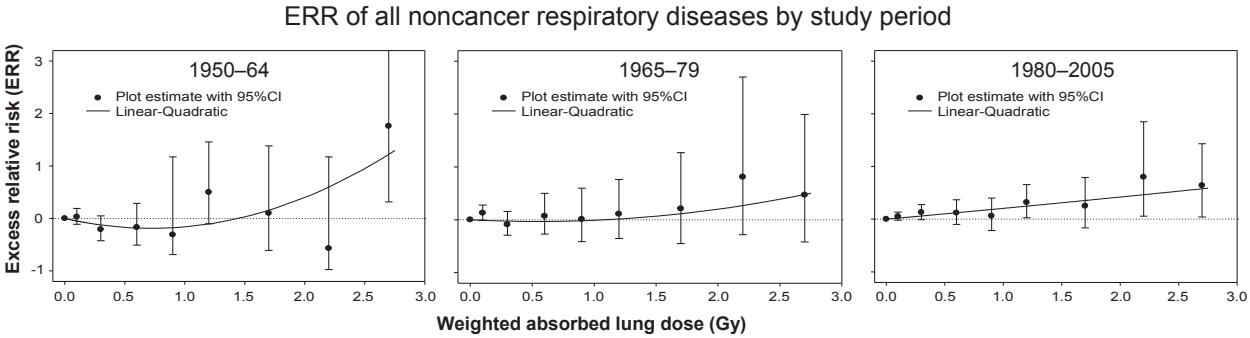
filtration rate) measurements in the AHS, was associated with CVD risk factors (hypertension, diabetes, hyperlipidemia, and metabolic syndrome), and with radiation dose (Sera et al., *Radiat Res* 2013; 179(1):46–52).

- 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 preclinical indicators of cardiovascular disease. Examples include: markers of chronic inflammation, insulin resistance or adipocytokines, such as TNF-α, IL-6, MCP-1, leptin, resistin, adiponectin, and IGF-1; physiological measurements reflecting atherosis (fatty deposits) or arterial stiffness; dilation of retinal veins and arterioles (indices of microvascular damage); visceral fat accumulation and fatty liver disease.
- Echocardiography: In the AHS we are planning echocardiographic measurements of A-bomb survivors to evaluate preclinical heart dysfunction that may be associated with valvular disease, ischemic heart disease, and heart failure.
- Are LSS radiation-CVD mortality results confounded by the healthy survivor effect?: We have collaborated with researchers from Helmholtz Zentrum München in an analysis that found no evidence that a healthy survivor effect had distorted the radiation dose-response curve for CVD effects (Schöllnberger et al., *Radiat Prot Dosim* 2014; doi:10.1093/rpd/nc0000).
- Radiation, smoking and microvascular changes: The diameters of retinal veins and arteries can be markers for radiation damage to microvessels of the circulatory system. A study has indicated that the impact of smoking on retinal venular dilation is reversible following long-term smoking cessation (Yanagi et al., *Invest Ophthalmol Vis Sci* 2014; 55(1):405–11). The associations of retinal venular and artery caliber with radiation are being analyzed.
- Experimental circulatory disease: To help confirm the A-bomb studies suggesting that circulatory diseases may be caused by radiation at moderate doses, we are seeking to validate the epidemiologic and clinical findings with an experimental study using strains of rats that are susceptible to hypertension and stroke. The study is examining doses down to 0.25 Gy, with endpoints of early stroke symptoms and mortality, a pathologic analysis of relevant organs/tissues, blood pressures, and biochemical measurements related to CVD risk.

Radiation and health outcomes other than cancer or circulatory disease

The A-bomb radiation exposure has been related to a variety of additional health outcomes. Several studies have been published this year.

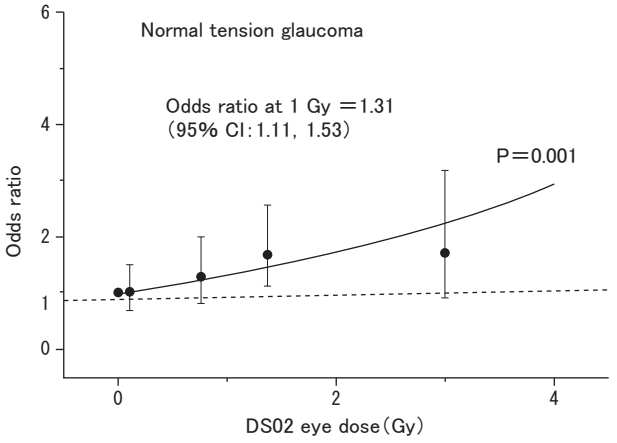
- Respiratory diseases: Prior LSS epidemiologic analyses had suggested an association between A-bomb radiation exposure and noncancer respiratory disease mortality. This study aimed to obtain insights regarding the degree to which the association reflects a diagnostic/epidemiologic artifact versus a genuine radiation effect. The study found that a substantial fraction of the association of noncancer respiratory disease mortality with radiation could be accounted for by prior or concurrent cancer or cardiovascular disease, which probably reflects misdiagnosis (Pham et al., *Radiat Res* 2013; 180:539–45) (Figure 5). There was no evidence of confounding by lifestyle variables.
- Radiation, body mass index (BMI) and muscle mass index: BMI and lean body mass (assessed by DXA) tended to decrease with increased radiation dose (Tatsukawa et al., *Int J Obes* 2013; 37:1123–8).
- Radiation and glaucoma: A screening study investigated whether radiation was associated with glaucoma prevalence. It found that radiation may be related to the



Hazard ratio (HR) adjusted for potential confounding factors (smoking, alcohol consumption, body mass index, education, diabetes, and occupation)			
	Not adjusted for cancer or CVD	Adjusted for cancer	Adjusted for cancer and CVD
All noncancer respiratory diseases	1.19 (1.09, 1.29)	1.12 (1.02, 1.24)	1.12 (1.00, 1.25)

(Pham et al., *Radiat Res* 2013; 180:539–45)

Figure 5. Radiation risk of mortality diagnosed as noncancer respiratory disease, 1950–2005



(Kiuchi et al., *Radiat Res* 2013; 180:422–30)

Figure 6. Radiation dose and prevalence of normal-tension glaucoma in A-bomb survivors

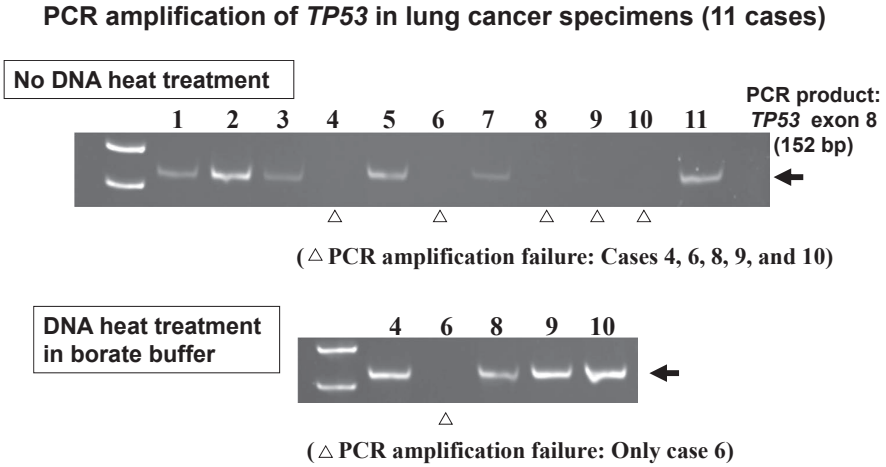
prevalence of normal tension glaucoma (Figure 6), but not glaucoma with elevated eye pressure. However, methodologic uncertainties limit the conclusions that can be drawn (Kiuchi et al., *Radiat Res*, 2013; 180:422–30).

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 nearly complete through 2012 in both Hiroshima and Nagasaki prefectures. Case abstraction from medical records has been completed through 2011 in both areas, and abstraction of the more recent cases is underway.
- Ongoing F_1 clinical examinations: The longitudinal clinical assessment of F_1 offspring of A-bomb survivors was begun in November 2010 on a four-year cycle. The repeat participation rate among those who were initially examined in 2002–2006 is about 82%. It is expected that this second round of examinations will be completed during FY2014.
- 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 needed.
- Tissue specimen access: A database that indexes RERF specimens of formalin-fixed paraffin-embedded tissues is being developed for future specimen utilization as part of our Biospecimen Repository. A system to preserve surgically resected materials from the A-bomb survivors in Hiroshima and Nagasaki areas is being worked out with community and university hospitals.
- Research data documentation: It is now required to submit documented analytic datasets to the Information Technology Department before study publication, so that RERF can be assured of having a record of the data on which its reports are based.
- Improved assays for old tissue samples: Because the A-bomb studies have been ongoing for more than 60 years, many of the stored tissue samples are old and sometimes partially degraded. A technique was developed that increases sensitivity in conducting PCR amplification, one of the fundamental, most widely used methods in molecular biology, which will be particularly useful with our old tissue samples (Taga et al., *Int J Clin Exp Pathol* 2013; 6:76–9) (Figure 7).
- Biosample Center: Planning and preparations have been conducted for the Biosample Center to become fully operational in FY2014. This will initially involve the integration of blood and urine biospecimens in a centralized facility, with accompanying database management to facilitate inventories and access.

(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,



(Taga et al., *Int J Clin Exp Pathol* 2013; 6:76–9)

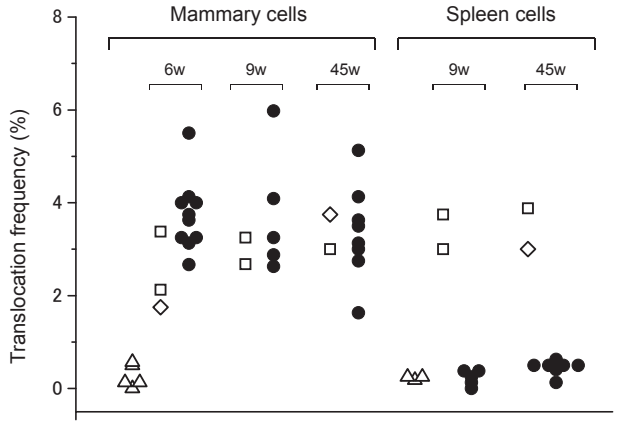
Figure 7. Preheating DNA in borate buffer facilitates PCR-based molecular analyses in old cancer tissue specimens preserved by the usual methods (formalin-fixed paraffin-embedded)

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 other genetic cancer mechanisms: The radiation dose response of *GPA* mutation frequency was found to vary by *p53BP1* polymorphism (Yoshida et al., *Mutat Res-Gen Tox Env* 2013; 755:49–54), suggesting that somatic mutability following radiation exposure may be partly dependent on individual variations in DNA double-strand break repair capability.
- 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 changing 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.
- Cytogenetic studies following fetal irradiation: Although lymphocytes from maternal irradiation of atomic bomb survivors and mice show dose-related chromosome translocations, those from their fetally exposed offspring do not. However, we have now found that both rat mammary-tissue cells (Nakano et al., *Radiat Res* 2014; 181:172–6) (Figure 8) and mouse thyroid epithelial cells (unpublished data) do show translocations after fetal exposure. The results are similar to our findings about the tissue-dependent induction of malignancies among the *in utero* exposed.
- Radiation and cancer mechanisms: Ongoing cancer studies aim to clarify mechanistic relationships between radiation exposure and cancer development among A-bomb survivors. Early molecular events in the development of cancers in the LSS cohort are being conducted, particularly studies of gene rearrangements in thyroid cancer, mutator phenotypes in colorectal cancer, and lung cancer mutations in radiation-exposed survivors.

Past RERF immunology studies determined that both immune cell counts and immune function were compromised by radiation. Current studies include the following:

- 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 have not yet been completed on the association of radiation dose with influenza vaccination antibody titers.
- Radiation and chronic oxidative stress: Intracellular reactive oxygen species levels, especially $O_2^{\cdot-}$ levels, in lymphocyte and granulocyte fractions increased with age and radiation dose. In addition, $O_2^{\cdot-}$ levels in T cells, especially in $CD8^+$ T cells, increased with age and radiation dose.
- Mechanisms of radiation immune effects: Radiation effects on stem cells, dendritic cells and the thymus gland that may attenuate immune function are being studied (Kyoizumi et al., *J Immunol* 2013; 190:6164–72). Assays are nearly completed for the stem cells and dendritic cells, and the thymus study was recently begun.
- Obesity, inflammation, and immune cells: A reduction in newly produced T cells was significantly associated with increased body mass index and inflammation, 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:e91985) (Table).



(Nakano et al., *Radiat Res* 2014; 181:172–6)

Figure 8. Difference between chromosome aberration (translocation) frequencies in lymphocytes (spleen cells) versus mammary cells after fetal irradiation. Maternal and fetal translocation frequencies in mammary cell cultures or spleen cells in rats that were gamma irradiated with 2 Gy. Fetus irradiation (closed circle); mother, 12 weeks old (square); virgin, 12 weeks old (diamond shape); and nonirradiated control rats (triangle). The time intervals in weeks between irradiation and FISH translocation analyses are shown at the top of the figure. Each point was derived from scoring 800 cells.

Associations of CD4 TRECs with radiation dose, age, and obesity/inflammation indicators

Indicator	Effect	*P*-value
Radiation dose	-	0.73
Age	↓	0.001
BMI	↓	0.016
HbA1c	↓	0.010
CRP	↓	0.032
Diabetes	↓	0.001
Fatty liver	↓	0.014

TRECs: T-cell receptor excision circles, an endpoint of T-cell production

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

Table. Associations of the production of new T cells with radiation and indicators of obesity, inflammation and metabolic diseases. Atomic bomb survivors were examined for production of new (more bioactive) T cells, with the hypothesis that reduced T-cell production may contribute to an adverse metabolic/inflammatory status, which may be enhanced by radiation exposure. T-cell aging status was evaluated in terms of the ability to produce naïve T cells, i.e., T-cell receptor excision circles (TRECs) in CD4 T cells. Although there was no significant association between radiation dose and TRECs, TREC numbers were inversely associated with various obesity/inflammatory indicators, suggesting that those factors may be involved in the effectiveness of the human T-cell immune system.

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

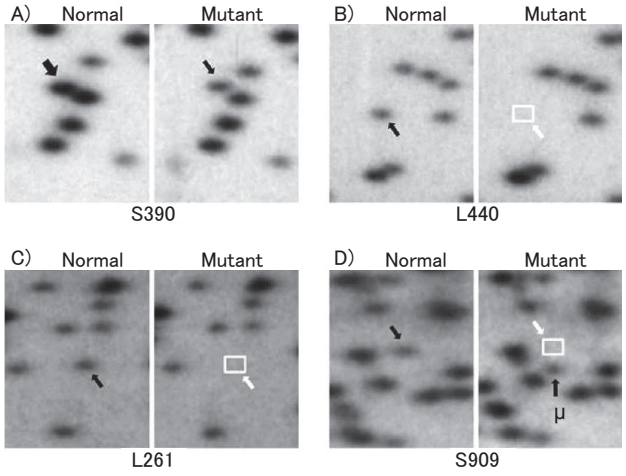
(1) F_1 mortality study and F_1 clinical study

- F_1 cohort study: A 14-year update of cancer and noncancer mortality risks in the epidemiologic cohort of 77,000 F_1 offspring of A-bomb survivors was submitted for RERF 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 are only beginning to experience the diseases of mid- and late-life. Continued follow-up for several more decades is therefore needed.
- F_1 noncancer genetic effects: Since many diseases besides cancer have a strong genetic component, we have been conducting a clinical study of about 12,000 children (F_1) of A-bomb survivors to study whether radiation impacts the frequency of various common non-cancer diseases. A paper showed no significant positive association between parental radiation exposure and the prevalence of multifactorial diseases/conditions in their offspring, including diabetes, hypercholesterolemia, hypertension, stroke, angina pectoris, and myocardial infarction (Tatsukawa et al., *J Radiol Prot* 2013; 33:281–93). However, the F_1 cohort will need to be followed up for several more decades because much of the incidence of these diseases occurs at older ages.

(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.

- Mutational model system: With an innovative genetically modified mouse model that we created, it is possible to see radiation-induced germ-cell (potentially heritable) mutations through expression of a mutant green fluorescent protein (GFP). We are working to develop a GFP system that can specifically target tumor-related genes. This may provide new insights about the genetic effects of radiation at low doses.
- Experimental estimation of the radiation-induced mutation rate: A study was published using restriction landmark genome scanning that could detect DNA deletions at about 1,200 genomic loci per mouse (Asakawa et al., *Radiat Res* 2013; 179:293–303) (Figure 9). Mouse offspring after a 4 Gy paternal dose showed marginally more deletions than the unirradiated-father group. Another study employed 2.1 million probes per genome using comparative genomic hybridization (CGH) technology to study *de novo* genomic deletions and duplications in the offspring that result from paternal radiation exposure. The study did not find any evidence of heritable radiation effects upon 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.
- Genetic study of A-bomb survivors using high-density microarray CGH analysis: A study of *de novo* mutations in the F_1 children of A-bomb survivors is underway, using a high density array of probes (1.4 million probes per individual) to detect genomic DNA deletions or duplications associated with parental radiation exposure. CGH analyses this year assessed 132 children and their parents along with molecular validation of candidate mutations.



(Asakawa et al., *Radiat Res* 2013; 179:293–303)

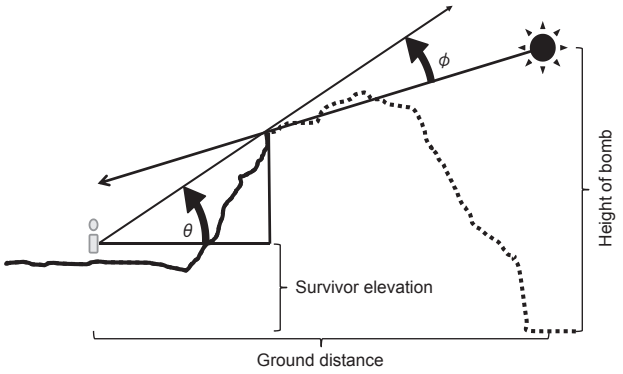
Figure 9. Examples of mutations found by Restriction Landmark Genome Scanning (RLGS) in mouse genomes in a study of the genetic effects of radiation. RLGS patterns from normal and mutant DNA in mice. Panel A: An example of the loss of one copy of DNA at a two copy spot (spot intensity was reduced by half). Panels B and C: Examples of the loss of a spot (indicated by white squares) that occurred at single copy spots. Panel D: An example of loss of a spot that accompanied a new spot (indicated by "μ") near the normal position (indicated by a white arrow), an indication of a mutation at a repeat sequence. The numbers indicated below each panel represent the spot IDs.

- Detectability of mutations by DNA sequencing: Two pilot studies are underway to develop expertise in using DNA sequencing to estimate radiation-induced mutation frequencies. The DNA from a cell line, with and without irradiation, was sequenced and analyzed to evaluate the detectability of indel (small) mutations, which may be significant for characterizing radiation mutation risk. The radiation-induced mutation rate in several F_1 mice is also being evaluated by whole genome sequencing; the bioinformatics data are being evaluated.

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 (using Geographic Information System technology) and structural shielding data of LSS study subjects has been completed. A greatly improved model of elevation and terrain shielding and its application to LSS subjects is nearly completed (Figure 10). Preliminary analyses suggest these changes will make relatively little difference overall in the risk estimates, but will reduce uncertainties and increase confidence in the dose calculations.
- Biodosimetry by electron spin resonance (ESR) of tooth



(Cullings et al., unpublished)

Figure 10. Both terrain profile and survivor elevation affect whether a survivor was partially shielded from the bomb radiation. This figure illustrates why the "grazing angle" θ to the terrain horizon for a survivor needs to be corrected for the elevation at the survivor's location in calculating terrain shielding. If the survivor and terrain are elevated, with the angle θ held constant, the angle ϕ related to the bomb changes, given that the height of the bomb explosion is held constant.

enamel: Molars from Nagasaki survivors showed good correlations among ESR dose estimates, DS02 eye doses, and the cytogenetic dose estimates on the same survivors. A summary report is nearly finished.

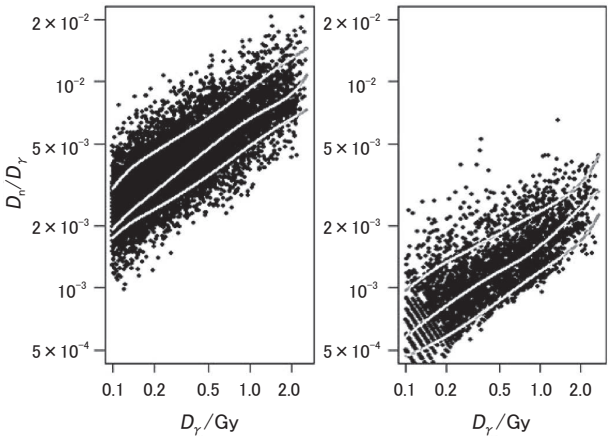
- Relative biological effectiveness (RBE) of neutrons: The impact of neutron doses from the bombs has continued to be of interest for risk assessment. We recently submitted a manuscript in collaboration with two outside experts. It identified an error in the way various outside investigators have calculated the RBE of the neutron component upon risks in the A-bomb study. The paper also evaluates how much various assumptions about RBE values for neutrons would influence the slope and shape of the dose-response associations (Figure 11).
- Dosimetry for "unknown dose" individuals: Two recent international workshops were held (February 2013 and February 2014) on the potential to derive doses for members of the LSS who had previously been assigned as "unknown dose," since a number of them were in proximal (<2 km from the hypocenter) locations, but in heavily shielded buildings or air-raid shelters. Examination of a series of building plans and their occupants showed that each building would require separate detailed dosimetric modeling. Given the relatively small number and imprecise locations of occupants in most such buildings, it was thought that any such modeling effort should be on a pilot basis only at this time. Visits were made to several bomb shelters that had recently been located to better determine what issues might be involved in estimating doses for the occupants.
- Fallout exposures: The RERF data are sparse and 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 will be reported. In comparing the mortality and cancer-incidence risks between the groups reporting "black rain" exposure or no exposure, no clear association with reported fallout exposure was seen. A paper summarizing the results is currently under review.
- Dose uncertainties: In the area of statistical modeling of dose uncertainties and the use of biodosimetric data to reduce uncertainties, we have extensive collaborations with three different external groups of statistical investigators. One paper is in press (Tekwe et al., *Stat Med* 2014) and another has been submitted.

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

- Low-dose risk uncertainties: The Statistics Department is developing a new method to examine risk uncertainties in dose-response data, particularly at low doses. The method provides more flexibility and less reliance on prior assumptions than the conventional methods.
- 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 wide applicability.
- Imputation of missing data: The Statistics Department is examining multiple imputation and other approaches to model missing data (missing for a fraction of the LSS cohort) in estimating the joint effects of radiation and smoking on lung cancer risk.

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

Efforts have been made to develop a number of



(Cullings, Pierce, and Kellerer, *Radiat Res*, submitted)

Figure 11. Ratios of neutron dose to γ-ray dose (D_n/D_γ), plotted by γ-ray dose for Hiroshima (left) and Nagasaki (right). The three white curves in each plot indicate the median and the 10%-ile and 90%-ile of the distribution of A-bomb survivors at each γ-ray dose. The plots show that neutron doses are a small fraction of gamma-ray doses for all survivors, and at low doses, where variable RBEs tend to become large, the relative size of the neutron dose is very small, so the effect of the variable RBE is minor.

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 involved in 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, skin, lung, lymphoid tissue, uterus, soft tissue/bone). The collaboration has led to numerous publications over the years, and research activities and mutual feedback will continue.
- 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 22 research institutions in North America, 12 research institutions in Europe, and 4 research institutions in Asia. We also have collaborations with investigators at 44 research institutions in Japan. All the research departments at RERF are engaged in such studies. We anticipate that more collaborative studies will be developed during FY2014 and beyond as opportunities, ideas, or needs develop.