Report of Major Activities

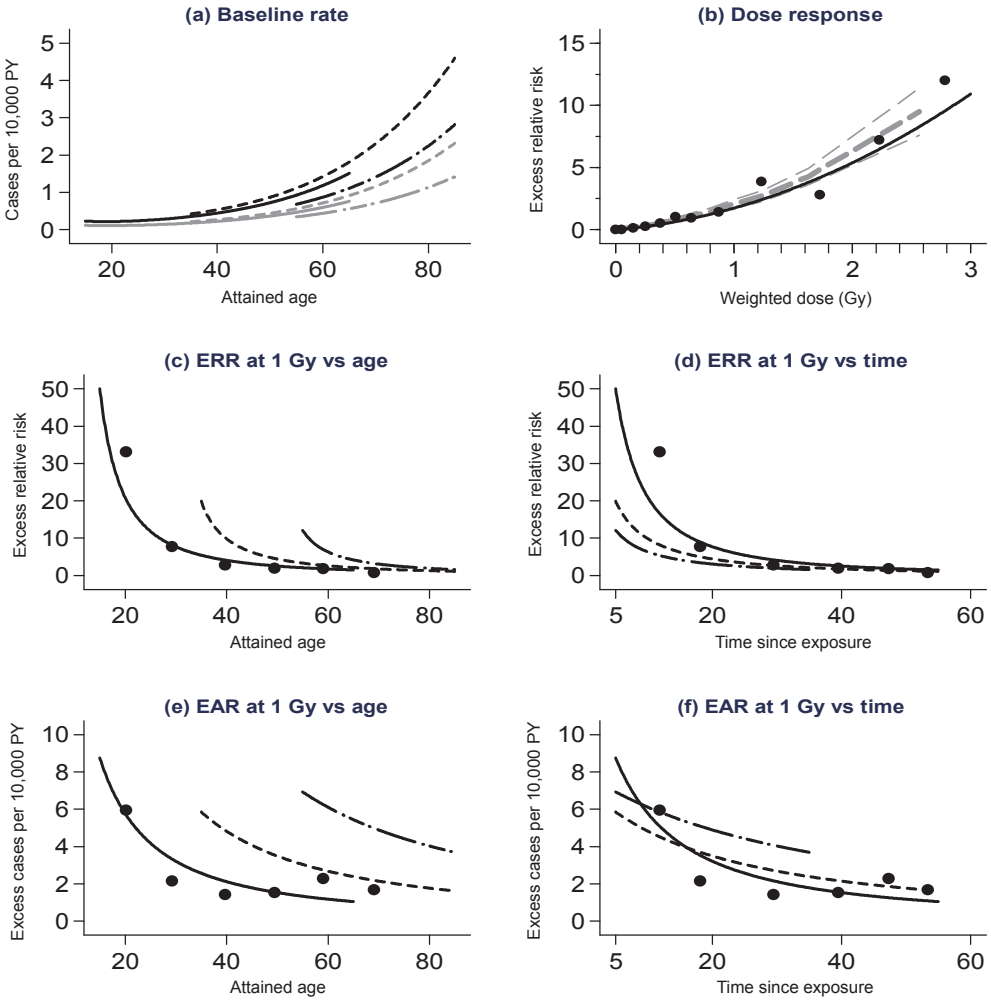
1. Research projects on A-bomb survivors' health

(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 55 years after the bombings. We continue to publish overview papers to inform the scientific community about the magnitude and characteristics of cancer effects from radiation (e.g., Okubo, *Radiat Prot Dosimetry* 2012; 151:671–3; Ozasa, *Child Health* 2012; 15:14–7 [Japanese]), and a number of new findings have been reported during FY2012.

- Leukemia: A paper updating the findings regarding radiation and the incidence of leukemia and other hematopoietic malignancies in the LSS showed that the dose response for all of the combined types of leukemia except CLL/ATL (chronic lymphocytic and adult T-cell leukemias, which have little or no association with radiation) was strongly linear quadratic (Hsu et al., *Radiat Res* 2013; 179:361–82) (see Figure 1). Even though it was previously thought that the leukemia risk was

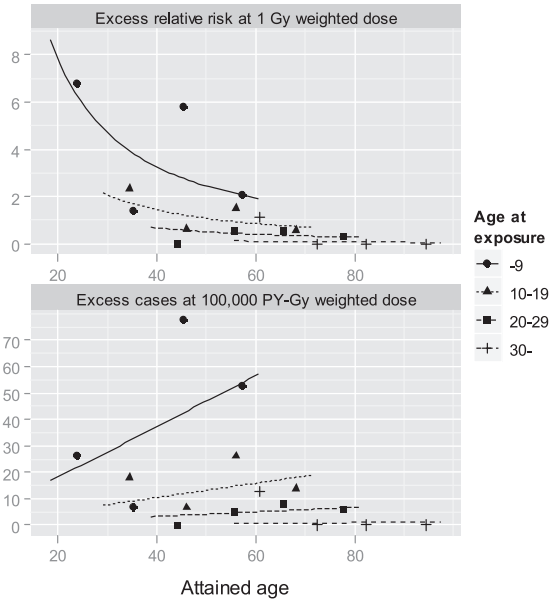


(Hsu et al., *Radiat Res* 2013; 179:361–82)

Figure 1. LSS leukemia risk (excluding CLL and ATL): Unexposed-baseline risks by birth cohort and sex (panel a); overall dose response (panel b); excess relative risk (ERR; panels c and d), and excess absolute risk (EAR; panels e and f) by age at exposure and age at risk or time since exposure
Panel a: Age-specific baseline (zero-dose) rates in Hiroshima for men (black lines) and women (gray lines) for those born in 1895 (dash-dot line), 1915 (dashed line), and 1935 (solid line).
Panel b: Radiation-dose response, ERR, standardized to attained age 70 for persons exposed at age 30. Solid-black line: Fitted linear-quadratic dose response. The individual (nonparametric) points are based on fitting dose categories simultaneously, while the middle-dashed-gray line is a smoothed version of the dose category-specific estimates. The dashed-gray lines are plus and minus one standard error from the smoothed fit.
Panels c and d: Temporal pattern and age-at-exposure effects for the ERR model, averaged across sex and city.
Panels e and f: Temporal pattern and age-at-exposure effects for Hiroshima males based on the EAR model. The individual points in panels e and f are nonparametric EAR estimates after exposure at age 10.

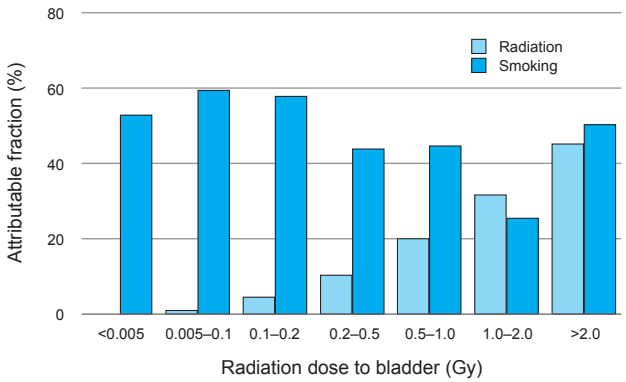
exhausted by about 30 years after irradiation, an excess risk has been observed in the LSS for 55 or more years after radiation exposure; this late-occurring leukemia risk was seen primarily for acute myeloid leukemia (AML). A suggestion of an elevated risk for non-Hodgkin lymphoma was seen among men, a result that merits cautious interpretation, because none was seen among females (RR at 1 gray [Gy] of 1.02). No radiation association was seen for either Hodgkin disease or multiple myeloma.

- Thyroid cancer: The thyroid cancer incidence data, with systematic pathological reviews, have been updated seven years, through 2005 (Furukawa et al., *Int J Cancer* 2013; 132:1222–6). The results show that there is a large risk for exposed children; for example, exposure to 1 Gy at age 5 leads to a 2.6–fold (95% confidence interval [CI]: 1.7–4.4) risk of thyroid cancer (see Figure 2). On the other hand, there is no clear evidence of excess risk from exposures after age 20. The excess thyroid cancer radiation risk is evident even at low doses and has persisted for more than 50 years, so it likely will continue for the lifetime.
- Urothelial cancers: The latest radiation and cancer report (Preston et al., *Radiat Res* 2007; 168:1–64) showed that one of the highest radiation relative risks was for bladder cancer. However, there was a question as to whether some of the imputed risk might actually be attributable to variations in smoking, alcohol consumption, diet, and sociodemographic or occupational factors. A more detailed analysis of urothelial cancers (>90% of which are bladder cancers) examining those possible co-factors has now shown that the radiation risk is virtually unchanged by them and is still strong. For instance, after adjusting for smoking, which is the strongest risk factor, the relative risk at 1 Gy was 1.99 (95% CI: 1.41–2.77), virtually identical to the risk estimate of 2.00 without adjustment (Grant et al., *Radiat Res* 2012; 177:86–98) (see Figure 3). There also was no evidence that the radiation risk for urothelial cancer was modified by any of the co-factors.
- Skin cancer: An analysis of updated radiation and skin cancer data shows that, unlike the approximately linear dose-response association for most types of solid cancer, there appears to be a dose threshold at about 0.6 Gy for basal cell skin cancer (Sugiyama et al., submitted, 2012) and a strong association above that threshold. There was little evidence that sunlight (ultraviolet) exposure modifies A-bomb radiation risk. There was no association of radiation with malignant melanoma or squamous cell skin cancer risk.
- Hormonal levels: We recently found that radiation dose is associated with alterations in estrogen levels, which in turn may mediate radiation-associated breast cancer risk (Grant et al., *Radiat Res* 2011; 176:678–87). Further analyses are underway to test that hypothesis.
- Breast cancer subtypes: We are conducting histoimmunological staining of breast cancer specimens to determine intrinsic subtypes according to estrogen and progesterone receptors (ER/PR) and Her2 (human epidermal growth factor 2), to determine whether certain subtypes are more sensitive to radiation effects.
- Colon cancer: It was thought that those who were obese might be at greater radiation risk for colon cancer, but analyses showed that this was not the case (Semmens et al., *Cancer Causes Control* 2012; 24:27–37).
- Liver cancer: The joint effects of radiation, hepatitis virus infection, alcohol consumption, chronic inflammation, and insulin resistance on hepatocellular cancer (HCC) risk are being examined, with particular interest in whether radiation effects are modified by the other factors. Besides a paper already published on hepatitis B or C infection, radiation, and HCC risk, another paper on inflammation, radiation, and HCC has been submitted and further analyses are underway.
- Lung cancer: A paper on how smoking modifies the radiation risk for various histological types of lung cancer



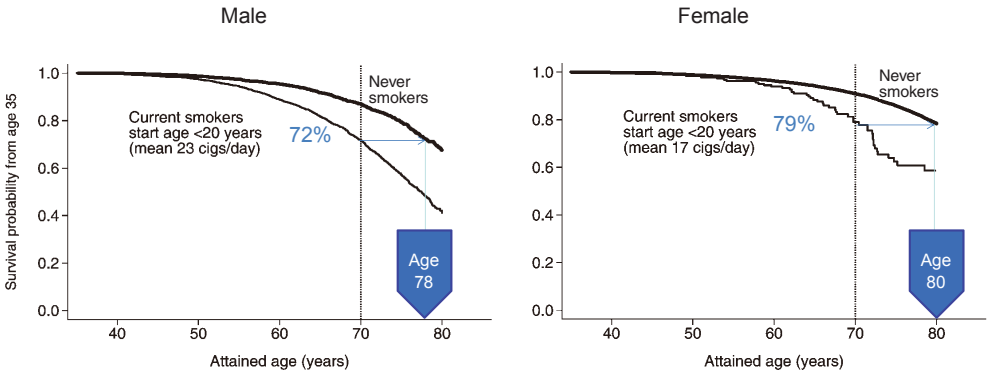
(Furukawa et al., *Int J Cancer* 2013; 132:1222–6)

Figure 2. Radiation-associated, gender-averaged risk for thyroid cancer in the LSS cohort by age-at-exposure and attained age (age at risk): ERR (upper panel) and EAR (lower panel) models. Four age-at-exposure curves for ages 5 (representing ages 0–9), 15 (10–19), 25 (20–29), and 41 (≥30) years. All curves and points are gender-averaged estimates.



(Grant et al., *Radiation Res* 2012; 177:86–98)

Figure 3. Attributable fraction of incident urothelial cancer cases to radiation and smoking in the LSS, 1958–2001, by radiation dose group (adjusted for sex and age)

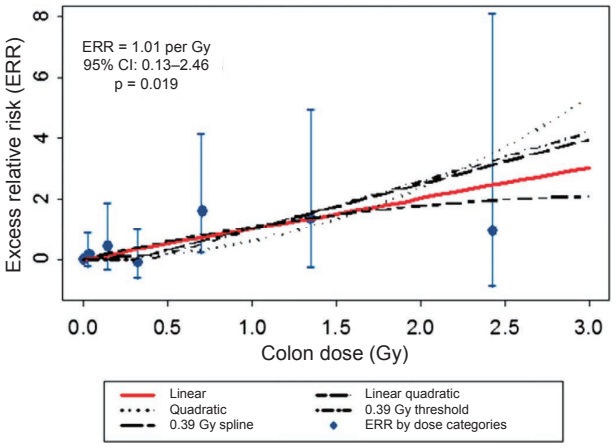


(R. Sakata, E. Grant et al., *BMJ* 2012; 345:e7093)

Figure 4. Effects of smoking on life expectancy in the LSS. Survival curves for never smokers and current smokers born 1920–1945 who started to smoke at age <20. Life expectancy was reduced by 8 years for males and 10 years for females.

was published (Egawa et al., *Radiat Res* 2012; 178:191–201), and more complex analyses are ongoing to further evaluate the joint association of lung cancer with smoking and radiation.

- Lung cancer and smoking: An important public health question has been whether cigarette smoking confers a much smaller effect on lung cancer risk among Japanese than among westerners, as some past studies have suggested. In a collaborative study with Oxford University, we showed that for groups with comparable ages at beginning smoking and similar amounts of smoking, the Japanese and western lung cancer risks are similar, and that smoking initiation before age 20 led to 8–10 years loss of life on average (Sakata et al., *BMJ* 2012; 345:e7093) (see Figure 4).
- Radiation and sarcomas: Although sarcomas have been seen following high doses from radiotherapy and from incorporation of certain bone-seeking radionuclides, the data are sparse regarding sarcomas from low and moderate external radiation doses. Last year we published a paper on bone sarcomas (Samartzis et al., *J Bone Joint Surg Am* 2011; 93:1008–15) showing an apparent dose threshold of about 0.8 Gy. We now have observed that for soft tissue sarcomas, which are more frequent than bone sarcomas, the dose response is approximately linear with a two-fold risk at 1 Gy (Samartzis et al., *J Bone Joint Surg Am* 2013; 95:222–9) (see Figure 5).
- Prenatal exposure: This is a unique study of disease experience in adulthood following prenatal radiation exposure. Since there are concerns about possible high risk for those exposed to radiation *in utero*, a paper on solid-cancer, leukemia, and non-cancer mortality for the *in utero* cohort is being prepared, comparing their risks with those following childhood exposure.
- Pathology reviews: Histological reviews are underway for a number of site-specific cancer studies, mostly conducted in conjunction with U.S. National Cancer Institute (NCI) investigators. Several address questions for which no information has previously been available. A histopathological study of uterine cancer will clearly discriminate for the first time in the A-bomb cohort the radiation risk for uterine corpus/endometrial cancer



(Samartzis et al., *J Bone Joint Surg Am* 2013; 95:222–9)

Figure 5. Radiation dose-response ERR modeling by ionizing radiation dose for soft tissue sarcomas in the LSS. Illustration of various ERR dose-response models in units of weighted Gy, with a relative weight of 10 for neutrons compared with gamma radiation. Baseline models were adjusted for age at the time of sarcoma diagnosis and year of birth.

compared to cervical cancer (diagnoses in the past were often labeled "uterus cancer" without further specification). A first histopathological review of malignant lymphoma will permit the examination of radiation risk for major subtypes, defined by immunophenotyping. Additional histopathological reviews on ovarian cancer and soft-tissue and bone tumors are underway.

- DNA damage: Since DNA damage that is unrepaired is believed to be a central feature of radiation-induced cancers, a study is being conducted to identify unique protein or biochemical signatures of unrepaired DNA double-strand breaks. Preliminary results were published this year (Noda et al., *J Cell Sci* 2012; 125:5280–7).
- Epigenetic effects: Not all of the damage from radiation that promotes cancer or other diseases is due to DNA alterations. Some is due to epigenetic effects—DNA methylation and histone modifications—which we have begun to examine.
- Prenatal exposure and mutations: A puzzling finding over

Table. Molecular analyses for *ALK* gene rearrangements in papillary thyroid cancers without other mutations,[§] by radiation exposure status

PTC case	*ALK* rearrangements		*P*[†]
	+	–	
Non-exposed (n = 6)	0	6	0.05
Exposed (>0 mGy, n = 19)	10	9	

[§] PTC carrying no mutations in *RET, NTRK1, BRAF,* and *RAS* genes
[†] Fisher's exact test

(Hamatani et al., *Thyroid* 2012; 22:1153–9)

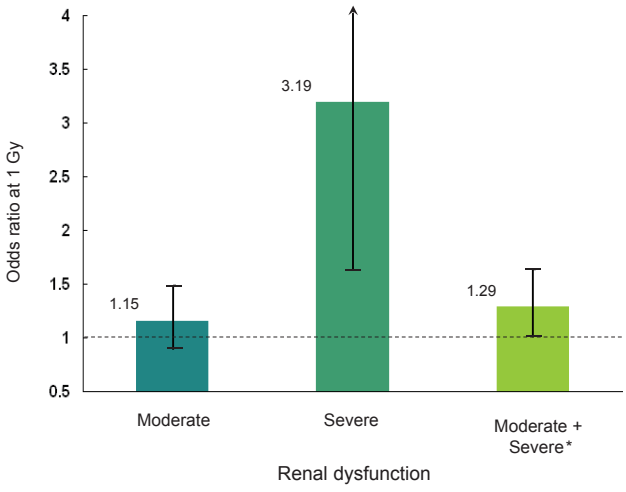
the years has been that virtually no leukemia risk was seen among those with *in utero* A-bomb radiation exposure. This prompted studies of chromosome translocation frequencies in lymphocytes in both humans and mice, which also showed no dose response after fetal A-bomb exposure, although a dose response was seen in the mothers. This suggested the presence of an *in utero* protective mechanism with regard to chromosome aberrations, and perhaps thereby protection against leukemia risk. However, it was found that radiation did cause chromosome translocations in rat mammary epithelial cells following fetal irradiation, suggesting that *in utero* mutation effects may be tissue-dependent. We are now seeking to confirm that hypothesis in mouse thyroid epithelial cells. These studies have potential implications regarding the nature of health risks from *in utero* exposure.

- Cancer mechanisms: Numerous studies are being conducted on the mechanisms of cancer induction by radiation. Rearrangements of the *RET/PTC* and *ALK* genes are being studied in papillary thyroid cancers from irradiated study subjects, with confirmation using a transgenic mouse model. This is the first report (Hamatani et al., *Thyroid* 2012; 22:1153–9) to show that *ALK* gene rearrangements are implicated in a fraction of radiation-associated thyroid cancers (see Table). Microsatellite instability and chromosome instability in colorectal cancers are being studied in relation to radiation dose. Radiation-related changes in gene expression will be studied in non-small cell lung cancer specimens.
- Immune factors and cancer: Studies of genes related to immunologic function and DNA repair are being conducted to explore the connections between radiation and cancer or other diseases. Reports are being prepared on immune-related genetic variants as modifiers of radiation risk for stomach cancer and colon cancer.

Radiation and circulatory disease risks

Because of new findings in the LSS regarding the association of radiation with circulatory diseases, the RERF Cardiovascular Disease Working Group has spurred the development and implementation of several new studies to learn more about the potential biological mechanisms by which low-to-moderate doses of radiation may confer cardiovascular and cerebrovascular disease risks. As part of this effort, we held an international workshop in February 2013 on radiation and cardiovascular disease risk that provided new insights on methods for study and mechanisms of radiation-related cardiovascular disease risk. Some highlights of our current work are given below.

- Arteriosclerosis: To better assess the association of radiation with arteriosclerosis and ischemic heart disease, physiological measurements of atherosis (fatty deposits) and arterial stiffness are being conducted. The diameter of retinal arterioles and veins also is being measured from retinal photos of AHS participants as an index of microvascular changes.
- Circulatory disease biomarkers: A variety of biomarker measurements are planned or underway of, for example, inflammation, oxidative stress, insulin resistance, endocrinologic (growth hormone) change, unstable plaque, subclinical heart failure, microvascular damage, and endothelial dysfunction.
- Stroke risk: A study reported a significant association between radiation dose and risk of hemorrhagic stroke, but not ischemic stroke (Takahashi et al., *BMJ Open* 2012; 2:e000654). However, there is a question as to the degree of risk at lower doses, which requires further study.
- Kidney function: Analyses have shown a relationship between radiation exposure and chronic kidney disease (Sera et al., *Radiat Res* 2013; 179:46–52) (see Figure 6). The next step is to determine the degree to which chronic kidney disease is an intermediate variable in the association between radiation and cardiovascular disease (CVD). An indication of increased risk of chronic kidney disease mortality also was observed in the epidemiologic LSS (Adams et al., *Radiat Res* 2012; 177:220–8).
- Echocardiography: In the AHS we are planning echocardiographic measurements of A-bomb survivors to evaluate preclinical heart dysfunction that may precede heart failure, since mortality from heart failure was related to radiation exposure in the LSS epidemiologic



(Sera et al., *Radiat Res* 2013; 179:46–52)

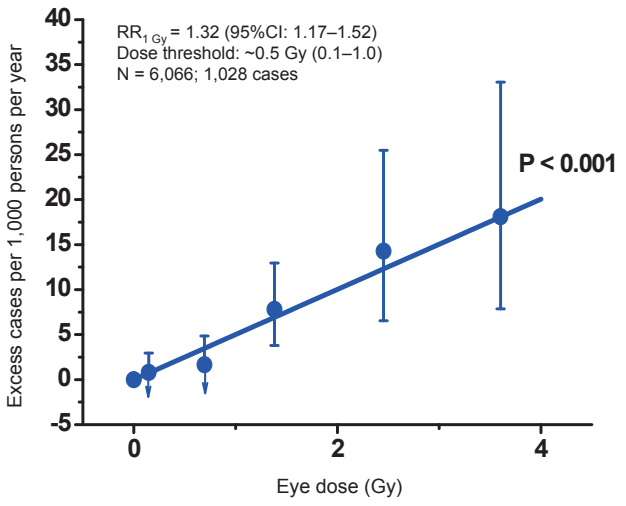
Figure 6. Relative risk of moderate and severe renal dysfunction (chronic kidney disease) at radiation dose of 1 Gy (adjusted for age, sex, smoking, alcohol, diabetes, hypertension, hyperlipidemia, and metabolic syndrome)

study. The measurements also will provide information regarding radiation and valvular disease.

- Animal model of stroke: To help validate the A-bomb studies suggesting that circulatory diseases are caused by radiation at moderate doses, we developed an experimental study of radiation effects on hypertension and stroke, using a strain of rats that is susceptible to those outcomes. A preliminary study examined doses of 1–4 Gy and found early radiogenic stroke mortality, even at 1 Gy. A larger study has been initiated to examine stroke, blood pressure, and circulatory disease biomarkers in rats at doses of 0.75, 0.5, and 0.25 Gy.

Radiation and health outcomes other than cancer or circulatory disease

- Cataracts: Radiation protection agencies had long believed there was no risk for vision-impairing cataracts below about 5 Gy and set safety standards accordingly. Based in substantial part on our recent data showing risks for clinically significant cataracts at doses well below 1 Gy (Neriishi et al., *Radiology* 2012; 265:167–74), the International Commission on Radiological Protection (ICRP) has now recommended a reduction in the dose limit to 0.5 Gy (see Figure 7).
- Cataract susceptibility: A study is underway to evaluate cataract progression among those with early/moderate opacities at the time of the 2000–2002 ocular examination program. The study will address an important, unanswered question in the radiation-cataract literature about the degree to which early opacities seen at low radiation doses progress to more advanced cataracts. We are also conducting a study on the role of genetic variation in susceptibility to radiation-associated cataract; the study centers on variants in DNA damage-repair genes that have been reported to confer increased susceptibility to radiation-induced cataracts in mice. Another program for the collection and storage of lens tissue samples from A-bomb survivors continues to collect such tissue for future molecular cataract studies.
- Retinal effects: Additional studies are underway to examine possible associations of radiation with glaucoma, retinal microvascular sclerosis, and macular degeneration. Preliminary analyses suggest that there may be associations of radiation with retinal venular sclerosis and normal-tension glaucoma, although subject-selection factors in the glaucoma study introduce uncertainty into that finding.
- Nonmalignant respiratory disease: Recent LSS reports have suggested a small association between radiation and the general rubric of nonmalignant respiratory disease. Analyses are being undertaken of the associations of radiation with more specific categories of nonmalignant respiratory diseases to clarify whether the radiation risks are genuine or the nominal associations arise from misdiagnosis and co-morbidity with cancer or cardiovascular disease. A paper has been submitted.
- Neurocognitive dysfunction: Early on, ABCC-RERF studies documented that radiation exposure to the fetus caused mental retardation and diminished IQ in children, but no information is available in the world literature on whether prenatal or early childhood exposure has additional detrimental mental effects later in life. We therefore are addressing that question with a new longitudinal study on neurocognitive dysfunction and dementia risk among those with fetal or early-childhood A-bomb exposure. Baseline measurements of neurocognitive function among those exposed prenatally or before age 13 in the AHS are nearing completion.
- Diabetes: Because mixed results were seen with regard to radiation and diabetes risk in a past study, a new study is now underway to determine if persons with certain *HLA* genetic patterns may have radiation risk for diabetes.



(Neriishi et al., *Radiology* 2012; 265:167–74)

Figure 7. Incidence of cataract surgery during 1986–2005 by radiation dose in the AHS (adjusted for city, gender, age at exposure, age at risk, and diabetes). Radiation protection agencies had long believed that there was no risk for vision-impairing cataracts below about 5 Gy and set safety standards accordingly. More protective safety standards for the eye (≤0.5 Gy) are now being implemented, largely because of the A-bomb data.

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

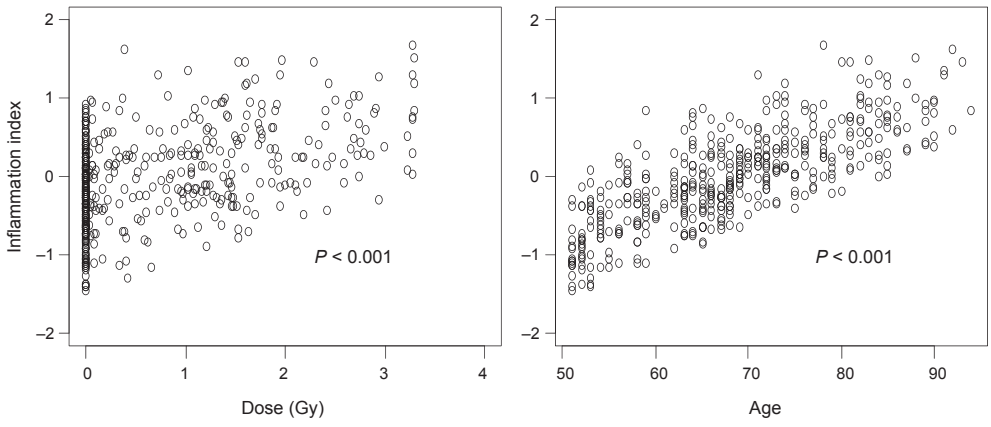
- Hiroshima and Nagasaki tumor/tissue registries: Case collection by notifications and death certificates is now complete through 2008 in both Hiroshima and Nagasaki, and detailed tumor rates have been reported to the International Agency for Research on Cancer for the new, updated version of "Cancer Incidence on Five Continents." Linkage between the registries and the RERF study cohorts has been completed through 2007, and the updated data will be used for various RERF studies of the LSS, *in utero*, and F_1 cohorts. The tumor registry database system developed at RERF is being adopted by many prefectures in Japan.
- Cancer incidence: Since we cannot directly identify which LSS cohort members reside in the Hiroshima and Nagasaki cancer registry areas, we rely on estimated numbers (by sex, age, time, city, and dose) for our cancer incidence studies using migration information from the AHS. The estimation methods and data are being updated in a collaborative effort between the Departments of Epidemiology and Statistics.

- Medical radiation exposures: The recent LSS mail survey updates and expands our information on potential confounding or effect-modifying factors for disease risk, such as lifestyle and sociodemographic variables. We plan to begin analyses of the information from the survey on medical diagnostic and therapeutic radiation exposures, to determine if such exposures are confounders of the A-bomb dose-response analyses.
- Tissue specimen access: Two initiatives regarding tissue specimens are underway. A database that indexes RERF specimens of formalin-fixed paraffin-embedded tissues is being developed to facilitate future specimen utilization. Research protocols for the development of a system to preserve surgical tissue specimens from A-bomb survivors in collaboration with community hospitals and universities in Hiroshima and Nagasaki have been implemented, and approvals from community hospitals for collaborative use of pathological materials are being sought.
- Research data documentation: It is now required to submit documented analytic datasets to the Information Technology Department before study publication to ensure that RERF has a record of the data on which its reports are based.
- Cryopreservation of samples: The immortalization of lymphocytes in Hiroshima AHS participants is nearing completion. Having expandable numbers of cells permits a variety of genetic and molecular studies to be conducted without permanently depleting blood-cell samples.
- Biosample Center: Plans have been made for a new Biosample Center that will serve as an integrated repository for RERF biosamples. Work also will begin on an integrated biosample database that is fashioned for research needs as well as for basic biosample management.

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

A number of 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.

- Mechanisms of radiation immune effects: RERF immunology studies have determined that both immune cell counts and immune function were compromised by radiation (Hayashi et al., *FASEB J* 2012; 26:4765–73) (see Figure 8). Additional studies of the health effects and mechanisms of radiation on immune function are in progress, as summarized below.
- Mechanisms of immune function: As part of a National Institute of Allergy and Infectious Diseases (NIAID)-supported project on radiation and immunologic function, we aim to determine the mechanisms of immune attenuation associated with radiation exposure—how radiation affects the stem cells, dendritic cells, and thymus gland that give rise to and activate mature immune cells. Additional assays include those for radiation-associated DNA damage (gamma-H2AX), aging (telomere length), and dysfunction (colony formation ability) of pertinent subsets of precursor immune cells.
- Integrated index of immune competence: Another of our aims is to develop an integrated scoring system for human immune competence to relate to radiation dose and disease incidence. Measurements of a large number of cytokine and immune markers to develop a robust immune-competence scoring system are being conducted for more than 3,000 A-bomb survivors in our AHS clinical study. The measurements, in progress, are being conducted jointly by investigators at RERF and Duke University.
- Vaccination response: A project to determine the effects of radiation on immune-responsiveness to influenza vaccination has now obtained before- and after-vaccination blood samples from more than 300 A-bomb survivors. Laboratory measurements of immunologic responses are underway jointly at RERF and Duke University. The study provides a window into the degree to which radiation-associated immune changes affect health status.
- Basic science workshops: We held an international workshop during March 2013 on DNA sequencing methods and their applicability to RERF research



(Hayashi et al., *FASEB J* 2012; 26:4765–73)

Figure 8. Integrated index of circulatory system inflammation by radiation dose and age in the AHS (individual data points are shown). Integrated index consisted of inflammatory biomarkers (ROS, IL-6, CRP, ESR).

questions about radiation effects in A-bomb survivors and their offspring. New collaborations are developing out of the workshop. We also published a meeting summary (Kodama et al., *Int J Radiat Biol* 2012; 88:501–6) of our international workshop on radiation and stem cell research held the previous year.

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 mortality: Since the F_1 epidemiologic cohort of 77,000 is still young and only beginning to experience the diseases of mid- and late-life, a continued follow-up for 30 or more years is anticipated. An analysis is underway to update the information on both cancer and noncancer mortality risk from parental radiation exposure for an additional nine years.
- 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 noncancer diseases. A paper was published on the relationship of parental radiation exposure to 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). There was no indication of a risk from parental radiation exposure for these diseases (see Figure 9).
- Ongoing F_1 clinical examinations: The longitudinal clinical study of the F_1 offspring of A-bomb survivors is in its third year (of a four-year cycle) of clinical examinations. A third meeting of the external oversight committee affirmed the direction and procedures of the study.
- F_1 mutations: 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 in relation to radiation exposure.

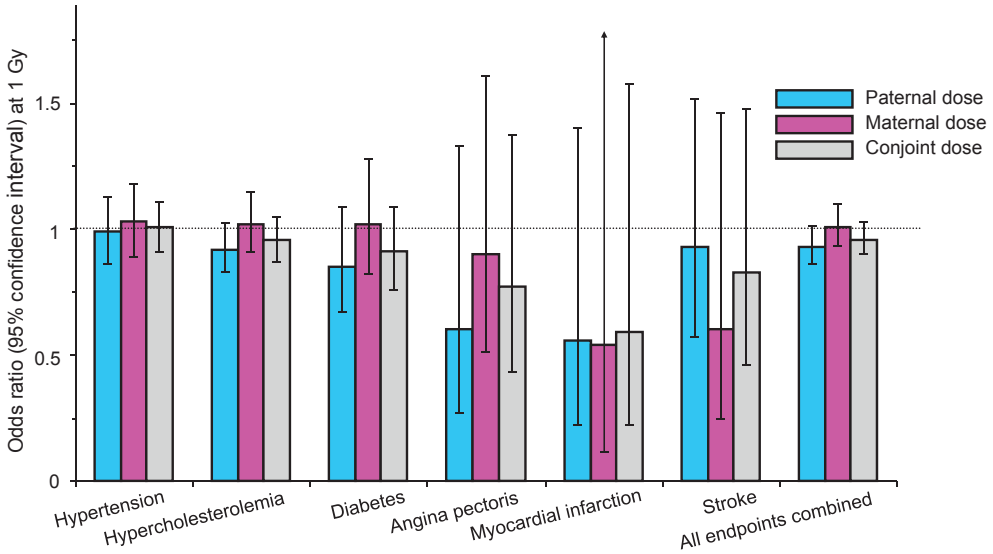
(2) Research on biological mechanisms related to the health of A-bomb survivors' children

- An experimental study to estimate the frequency of heritable mutations in irradiated mice by comparing mutations in irradiated fathers and their offspring using two-dimensional DNA electrophoresis has been published (Satoh et al., *J Biomed Biotechnol* 2012; Volume 2012, Article ID 789024, 10 pages) (see Figure 10).
- Experimental trans-generational mutation risk: A study is nearing completion that uses a state-of-the-art method to detect mutations in the offspring of mice exposed to a high dose of radiation. It employs 2.1 million probes per genome to study *de novo* copy number variants (CNVs, i.e., genomic deletions and duplications) throughout the genome. The study will provide the best evidence to date on the rate of genetic mutations from paternal irradiation.
- Mutational model system: With an innovative genetically modified mouse model that we created, we are able to see radiation-induced germ-cell (potentially heritable) mutations through expression of a mutant green fluorescent protein (GFP), and are working to develop a GFP system that can specifically target tumor-related genes. This development may provide new insights about genetic effects of radiation at low doses.

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

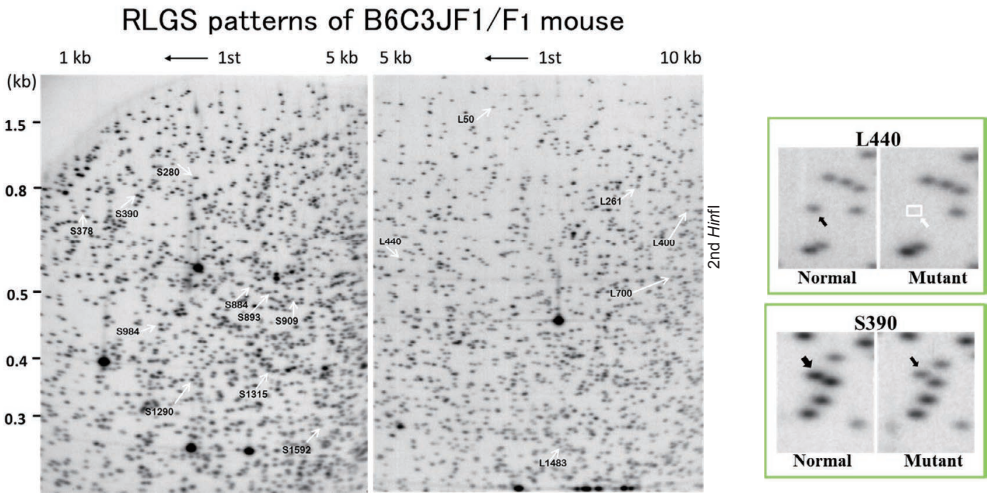
(1) Investigation of conditions required for dose estimates including survivor location, shielding effects, and organ dosimetry

- Based on our international workshop in 2011, we published 14 articles in *Radiation Protection and*



(Tatsukawa, Cologne, et al., *J Radiol Prot* 2013; 33:281–93)

Figure 9. Relative risk at a parental dose of 1 Gy for the prevalence of adult multifactorial diseases in the offspring of A-bomb survivors (adjusted for age, city, sex, BMI, parental multifactorial-disease history, menopause status [females only], alcohol drinking status, and employment status)



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

Figure 10. Example of detection of mutations in the offspring of irradiated male mice using two-dimensional DNA electrophoresis (small right-hand panels are blow-ups of mutation locations). The genetic risk in mice from radiation determined by estimate of the mutation induction rate per genome. Applied two-dimensional DNA electrophoresis to estimate the genetic risk in mice from radiation. Examined ~2,000 DNA locations in 1,000 offspring (500 born to 5 Gy irradiated spermatogonia and 500 controls) and found 5 deletion mutations in the exposed and 1 in the controls. Conclusion: 1 Gy of radiation will induce ~1 deletion per mouse genome.

Dosimetry (Vol. 149(1), 2012) which define how to make improvements in the estimates of organ doses for A-bomb survivors in the LSS and AHS. The articles point the way for new computational methods and models of the human body from contemporary medical imaging technology, which will permit more accurate organ dose estimates, extend the number of organs for which doses can be estimated, and improve estimates for those with partial body shielding (e.g., factory workers in Nagasaki).

- Improved organ dosimetry: Approval was given to initiate a program to develop the needed components for improved organ dose estimation. This will require efforts by both RERF members and external consultants.
- Survivor location: Work has been completed under the RERF Dosimetry Committee to improve survivor location information. LSS subject locations have been pinpointed using an electronic geographic information system (GIS) and new, more accurate and detailed maps of Hiroshima and Nagasaki. Other aspects of the individual dosimetry system (e.g., improved corrections for elevation and terrain shielding) are nearing completion.
- Dosimetry for "unknown dose" individuals: An international workshop was held during February 2013 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 locations (<2 km from the hypocenter), 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, at this time, any such modeling effort should be made on a pilot basis only.
- 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, a number of analyses to determine if "black rain" accounts for observed health effects have been undertaken and will be reported. Analyses of spatial patterns of fallout and reported epilation (hair loss; a high-dose phenomenon) do not suggest a correlation between the two. The mortality and cancer-incidence risks are being investigated between the groups reporting "black rain" exposure or no exposure, with statistical control for direct A-bomb dose level. We expect to submit one or more papers on these matters during the next year.
- Dose uncertainties: In the area of statistical modeling of dose uncertainties, we have extensive collaborations with three different external groups of statistical investigators. Two RERF collaborative papers on the estimation of dose uncertainty have been submitted for publication and a third paper is expected.
- 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 collaborative manuscript for publication with Dr. D. Pierce (Oregon Health and Science University) and Dr. A. Kellerer (Ludwig-Maximilian University). The paper evaluates how much various assumptions about RBE values for neutrons would influence the slope and shape of the dose-response associations.
- A review of the use of A-bomb survivors' tooth enamel to estimate A-bomb gamma and neutron doses was published (Nakamura et al., *Radiat Prot Dosimetry* 2012; 149:79–83).

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

- 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.
- Collaborations with several European statistical groups are underway to develop mechanistic statistical models of radiation effects on leukemia and lung cancer, and to explore multi-model inference regarding radiation effects on breast cancer (Kaiser et al., *Radiat Environ Biophys* 2012; 51:1–14) and on cardiovascular disease.
- The Statistics Department is examining multiple imputation and other approaches to model missing data in estimating the joint effects of radiation and smoking on lung cancer risk.

4. Collaboration 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. NIAID

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

(2) Collaboration with the U.S. NCI

Site-specific cancer incidence studies (female breast, skin, thyroid, lung, ovary, lymphoid tissue, uterus, soft tissue/bone). The partnership has led to numerous publications over the years.

(3) Radiation research partnership program with the University of Washington and Kurume University

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. The partnership led to a new U.S. National Institutes of Health (NIH) grant and to three published papers during FY2012.

(4) Facilitation of ongoing domestic and international collaborative studies with investigators at:

- 39 research institutions in Japan
- 18 research institutions in two countries in North America
- 11 research institutions in four countries in Europe
- 6 research institutions in three countries in Asia

(5) Additional international collaborations

- Continuation of activities as a World Health Organization (WHO) Collaborating Centre and for the WHO Radiation Emergency Medical Preparedness and Assistance Network (REMPAN).
- Dispatch of researchers to such scientific committees as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission on Radiological Protection (ICRP).
- Continuation of negotiations for designation as a collaborative organization of the International Atomic Energy Agency (IAEA). Cooperation as a member of the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) for realization of a collaborative project between HICARE and IAEA.
- Participation on scientific sub-committees or task groups for such international organizations as the IAEA, WHO, UNSCEAR, ICRP, and NCRP (U.S. National Council on Radiation Protection and Measurements).