Cross-sectional study of the association between radiation exposure and body mass index or body composition in Hiroshima atomic-bomb survivors

There is no precedent for research examining whether or not exposure to atomic-bomb (A-bomb) radiation affects obesity and body composition. This study first reviewed the association between radiation exposure and body mass index (BMI) among 2,686 Hiroshima A-bomb survivors (834 males and 1,852 females), all of whom participated in the Adult Health Study (AHS) during the period from 1994 through 1996. The results of the study indicate that BMI tended to decrease with an increase of radiation dose in both sexes. Among males who were less than 15 years of age at the time of radiation exposure, an increase in radiation dose was significantly associated with a decrease in BMI. We also examined the association between radiation exposure and body composition among 1,729 A-bomb survivors (550 males and 1,179 females), who were assessed with whole-body dual-energy X-ray absorptiometry. As in the case of BMI, the muscle mass index (appendicular lean mass/height^2) tended to decrease with an increase of radiation dose among males who were less than 15 years of age at the time of exposure. Furthermore, the abdominal fat index (trunk-to-limb fat ratio) increased with an increase of radiation dose among females who were less than 15 years of age at the time of exposure. This study suggests decreases in BMI and alterations in body composition with increased radiation dose among A-bomb survivors around 50 years after the A-bombings.

The association between chronic kidney disease and cardiovascular disease risk factors in A-bomb survivors: Cross-sectional study

A-bomb radiation is associated with cardiovascular disease (CVD) and metabolic CVD risk factors. Chronic kidney disease (CKD) is also known to be a risk factor for CVD, but little is known regarding whether CKD is associated with A-bomb radiation. To examine whether CKD is associated with CVD risk factors or A-bomb radiation in A-bomb survivors, we classified renal dysfunction according to estimated glomerular filtration rate (eGFR) in 1,040 Nagasaki AHS subjects who were examined in 2004–2007 as normal, mild, moderate, or severe. We diagnosed subjects in the moderate and severe renal dysfunction group as having CKD (eGFR <60 and <30 ml/min/1.73 m^2, respectively).

We looked for an association between CKD (moderate or severe renal dysfunction) and hypertension, diabetes mellitus, hyperlipidemia, and metabolic syndrome. CKD and severe renal dysfunction were significantly associated with radiation dose, and the odds ratios per Gy were 1.29 (95% confidence interval [CI], 1.01–1.63, P = 0.038) and 3.19 (95% CI, 1.63–6.25, P < 0.001), respectively.

A study on chromosome aberrations induced in mouse thyroid cells following fetal X-ray irradiation

We previously reported that translocation frequency in adult rats following fetal irradiation in mammary cells was nearly the same as that of their mothers, while almost no aberrations were detected in either peripheral blood T lymphocytes from in utero exposed A-bomb survivors or mouse hematopoietic cells irradiated as fetuses (both examined in adulthood). Therefore, it is suggested that translocation frequency in adults following fetal irradiation may vary among tissues. To understand the tissue-dependency, we examined thyroid cells in adult mice irradiated as fetuses. The results showed that chromosome damage in mouse thyroid cells following fetal exposure persisted, as was seen in rat mammary cells. Thus, it is apparent that chromosome aberration induction by radiation is different between blood cells and non-blood cells such as mammary and thyroid epithelial cells. The results suggest that blood cells, which did not record such damage, may be unique among cell types.

An animal model for human female exposure; no indication for the transgenerational effects of radiation following exposure of immature oocytes of rats to 2.5 Gy of gamma rays

The estimate of radiation risk of mutation induction in mouse spermatogonia serves as a good model for human male exposure to radiation and has been used for the estimation of genetic risk of radiation in humans. In contrast, it has not been possible to use female mice as the model for human female exposure to radiation because the target cells, immature oocytes, are extremely sensitive to the killing effect of radiation. We found that female rats were indeed resistant to radiation and prepared F1 (offspring) rats derived from 2.5-Gy gamma irradiated Sprague-Dawley (SD) females mated with Brown-Norway (BN) male rats. We examined the spleen DNA of 750 F1 animals each from the exposed and the control groups by two-dimensional electrophoresis. We selected around 1,500 visualizable spots (loci) each from the SD and BN rats for mutation analyses. Thus far, we have analyzed about 2.2 million spots each derived from the maternal SD or paternal BN strains. We found a total of 24 mutations; 13 in the control and 11 in the exposed group. Most of the mutations, 20/24, occurred at microsatellite repeat sequences and were not regarded as radiation related. Two deletion mutations were found in the exposed group but both occurred on the paternal alleles. In summary, we have observed no indication for the transgenerational effects of radiation following exposure of immature rat oocytes to 2.5 Gy of gamma rays.

Virtualization of servers began last year, and that process is being carried forward. As a result, 25 virtual servers are currently in operation. The main databases are being transitioned to the newest software versions, and the research database has begun operation on a new virtual server. The lifecycles of Windows XP and Office 2003 software currently used within the Foundation will soon expire. A comprehensive contract has been concluded and preparations have been made for transition to Windows 7 and Office 2010.

To save labor through centralization of the materials handled by the Library and Archives Section, the Historical Archives Office has been moved to the Library. Retroactive data entry into the database owned by the Library has continued. Further, library management has initiated use of barcodes, and the card lending system has been discontinued. RERF has also been participating in the NACSIS-CAT/ILL (an inventory location information service) operated by the National Institute of Informatics. As a result, it has become easier to obtain copies of texts, and the number of requests for copies from other organizations has increased, leading to increased use of books.
### Radiobiology/Molecular Epidemiology

**Analysis of ALK gene rearrangements in lung adenocarcinoma among atomic-bomb survivors**

Constitutive activation of the RAS signaling pathway is one of the most important early events in lung carcinogenesis. Recently, ALK gene rearrangements, which activate the RAS signaling pathway in lung adenocarcinoma, have been reported among lung cancer cases. We examined whether ALK rearrangements, which could also be involved in the development of radiation-related lung adenocarcinoma, were detectable and analyzable among A-bomb survivors. ALK rearrangements were detected in five adenocarcinoma cases (three of which belonged to a radiation-exposed group of 10 cases and two of which to an unexposed group of 10), implying that archival cancer tissue specimens from A-bomb survivors can be used for the analysis of ALK rearrangements. However, analysis with a larger number of cases will be necessary in the future to clarify the association of ALK gene rearrangement with radiation exposure.

**Effects of NKG2D haplotypes on the cell-surface expression of NKG2D protein on natural killer and CD8 T cells of peripheral blood among atomic-bomb survivors**

NKG2D is an activating receptor that triggers cell-mediated cytotoxicity in natural killer (NK) cells and CD8 T cells, which play key roles in immunosurveillance mechanisms. We previously identified NKG2D haplotypes and reported that NK cell activities differing among individuals were in part affected by these haplotypes. This study found that NKG2D haplotypes correlated with cell-surface expression of NKG2D protein in NK and CD8 T cells of peripheral blood in atomic-bomb survivors. Our results imply that NKG2D haplotypes contribute to inter-individual variations in human cytotoxic response through NKG2D protein expression in these cells.

### Epidemiology

**Health risks of radiation among the atomic-bomb survivors**

The risk of radiation for thyroid cancer incidence increased linearly compared to non-exposure by 128% at age 60 after exposure to atomic-bomb radiation of 1 Gy at age 10 in the Life Span Study (LSS) (collaboration with the U.S. National Cancer Institute [NCI] and RERF Statistics Department). For incidence of basal cell skin cancer, there appears to be a dose threshold at about 0.6 Gy and a strong association above that threshold (collaboration with NCI). For incidence of soft tissue sarcomas, the dose response is approximately linear with a 101% increase at 1 Gy compared to non-exposure (collaboration with the University of Hong Kong). In the area of dosimetry, members of the Epidemiology Department contributed to the activities of RERF’s Committee on Dosimetry, particularly in leading the effort to improve the precision of location information at the time of bombing for the LSS subjects that was estimated from the interview surveys in the early period after the bombing.

**Health effects of smoking**

It had long been doubted if the effects of cigarette smoking on lung cancer could be weaker in Japanese people than westerners. Therefore, the risk of smoking was evaluated in the LSS, in which people have been followed up as long as the classic British Doctors Study. For groups with comparable ages at starting smoking and similar amounts of smoking, the Japanese and western lung cancer risks were found to be similar, with smoking initiation before age 20 leading to 8–10 years loss of life on average (collaboration with Oxford University).

### Statistics

**Radiation risk assessment and dosimetry**

Members of the Statistics Department published several first- and second-author papers on risk assessment, including papers on the long-term trend in risk of thyroid cancer, incidence of cataract surgery, and multifactorial diseases of adulthood in the offspring of the atomic-bomb survivors. Moreover, a member of the department gave an invited talk on the impact on the offspring of the atomic-bomb survivors. Members of the department gave an invited talk on the impact on the radiobiology/Molecular Epidemiology.

**Statistical methodology for other RERF studies**

Members of the Statistics Department consulted at the inception of numerous studies, such as a current study of circulatory disease in animal models using irradiation at relatively low doses, contributed to subject selection and planning analyses for several studies of the effects of radiation and aging under the U.S. National Institute of Allergy and Infectious Diseases (NIAID) grant, and participated in the Epidemiology Department’s new collaboration with NCI on an extensive new analysis of cancer incidence. The Statistics Department provided analytical support for a large number of RERF studies during the year, including at least 17 published or submitted manuscripts and numerous presentations at scientific meetings.
Effects of interleukin-10 haplotype and atomic-bomb radiation exposure on gastric cancer risk

In a cohort study of gastric cancer (GC) among atomic-bomb survivors, we examined the radiation dose response of GC risk according to interleukin-10 (IL-10) haplotype, which was determined on the basis of polymorphisms of the inflammation-related IL-10 gene. When dividing GC cases into intestinal and diffuse types, we found that the dose response of diffuse-type GC risk differed according to IL-10 haplotype, but there was no significant association between intestinal-type GC risk and radiation dose in persons with any IL-10 haplotype. These results imply that IL-10 gene polymorphisms are involved in the inter-individual variation of radiation-associated diffuse-type GC risk.
A clinical study of the F₁ offspring of A-bomb survivors was conducted from 2002 through 2006 to examine the effects of parental radiation exposure on prevalence of adult-onset multifactorial diseases among F₁ subjects. The results of this study were published in a 2008 report. In the study, however, the average age of the F₁ subjects who underwent health examinations was young, at 49 years, just at the beginning of the age range in which diseases frequently occur. At the same time, the possible presence of cross-sectional study bias could not be ruled out. Thus, the Scientific and Ethics Committees for the Health Effects Study of the Children of A-bomb Survivors, the Scientific Council, and the Senior Review Panel recommended that a longitudinal study be conducted. Based on these recommendations, RERF’s F₁ Clinical Study Working Group, consisting of the Vice Chairman, an executive director, chief scientists, department chiefs, and research scientists, had discussions to develop a new research plan, which was completed in FY2009. This research plan was approved by the first meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors in July 2010, and the longitudinal study commenced in November 2010, with the collaboration of the Departments of Epidemiology and Information Technology, as well as other departments.

The participation rate during the two-year period following the start of the aforementioned longitudinal study was 76.0% (about 5,100 participants), an increase of about 7% compared with the first-year figure of 69.2%. Furthermore, we performed analyses of individual multifactorial diseases using data obtained from the previous clinical study of disease prevalence. Based on these analysis results, we reported in the *Journal of Radiological Protection* in 2013 that there was no evidence indicating an increase in risk of any of these individual diseases among the offspring of the A-bomb survivors due to paternal or maternal radiation exposure.

Among the duties assigned to the Dosimetry Committee, which was established in FY2009, the correction of survivors’ exposure locations was nearly completed in FY2012.

First, the committee obtained aerial photographs taken immediately before the bombings to correct the distortion of U.S. Army maps used to determine the hypocenters and survivors’ locations. By making adjustment for shooting angles, elevation, lens aberration, and the altitude of objects, aerial orthophotographic maps, which provided integrated plain views covering all areas of both cities, were prepared, and it was decided that they should be used hereafter as standard maps for showing exposure locations.

About 100 common geographic target points in each of the two cities were set on the U.S. Army maps and on these aerial photographic maps. For respective triangle areas formed by these points, conversion equations were used to systematically convert coordinates on the U.S. Army maps to new coordinates.

Neighborhood drawings indicating shielding histories were available for about 28,000 cases. These neighborhood drawings and aerial photographs were superimposed using up-to-date GIS (geospatial information system) computer software, to determine accurate exposure locations. This analysis was performed by two employees working independently of each other to gauge the accuracy of the process. Accuracy of identification was found to be high, as the difference between the locations identified by the two workers was less than 2 m in most cases.

In performing this analysis, we found that the fourth digits of some coordinates of exposure locations entered into the original database had been rounded down, while the fourth digits of other coordinates had been entered. Therefore, modifications were made to enter all the coordinates in four digits.

As a result of this modification, substantial changes were made in individual doses, as estimated doses in a few cases were even altered by more than several hundred milligray. However, these errors were random, and the average doses did not change. The recalculation did not change at all radiation risk of all the solid cancers combined. However, in future analyses to be conducted using more detailed disease categories, significant changes may occur in some categories.