

## Departmental Overview

RERF aims to characterize and quantify the late health effects of radiation using data from the atomic-bomb survivors. The Department of Epidemiology's follow-up of the Life Span Study (LSS) of survivors, the *in utero* cohort, and the F<sub>1</sub> cohort (offspring conceived after the bombing) is crucial to accomplishing these purposes. Follow-up outcomes include deaths of survivors and causes of death wherever they may occur in Japan and cancer incidence in Hiroshima and Nagasaki prefectures, where a large percentage of the survivors still dwell. Histological specimens of cancer cases have been used for patho-epidemiological studies in collaboration with community pathologists who keep those materials. Around 29% of the LSS cohort members were still alive at the end of 2014, including 77% of those who were less than 10 years old at the time of bombing (ATB). Moreover, 78% of the *in utero* and 89% of the F<sub>1</sub> cohorts are still alive. Therefore, continued follow-up of these young age groups for an additional 20 years or more is clearly essential. Important aims are to investigate consistency between epidemiological evidence and biological mechanisms of radiation effects, to epidemiologically evaluate other risk factors for confounding or modification of radiation risks, and to more precisely determine the magnitude of risk for radiosensitive subgroups such as those who were in early childhood or *in utero* at the time of exposure. For these F<sub>1</sub> studies we are developing an integrated program in the Genetics Research Cluster.

International risk assessment groups use the results from these cohorts as the primary basis for radiation-risk estimation because the data are unparalleled, representing a large cohort of all ages with a wide range of well characterized doses and a long-term, high-quality disease follow-up. The LSS mortality and incidence data of those cohorts have been periodically analyzed. Major results from our studies are heavily relied upon for the creation of numerous radiation-risk reports, including by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2006, 2013), the International Commission on Radiological Protection (ICRP) (2007, 2012), and the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (BEIR) VII (2005). Findings by the Epidemiology Department in recent years that have been of particular importance to the radiation protection and risk-assessment community have pertained to the magnitude of risk per unit radiation dose for leukemia, total solid cancer, and a variety of solid cancer sites; the shapes of dose-response curves; the way in which cancer risk varies by gender, age at radiation exposure, time since exposure, and age at risk; effect modification—whether radiation effects multiply or only add to disease risks from other risk factors (e.g., smoking); risk of cardiovascular and respiratory disease death from radiation; disease risks among those who received prenatal radiation exposure; and disease risks in the offspring of exposed parents.

High-quality cancer-incidence data in Hiroshima and Nagasaki have been periodically published in “Cancer Incidence in Five Continents (CI5)” (by the International Agency for Research on Cancer [IARC]/International Association of Cancer Registries [IACR]), a compilation of worldwide cancer incidence data, and are given the highest rating by that consortium. The data on childhood cancer were also used in the “International Incidence of Childhood Cancer, Volume 3 (IICC-3)” (by IARC/IACR) and the CONCORD-3 (a global comparison of population-based cancer survival).

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**FY2018 Achievements*****Radiation and Cancer in the LSS***

- *Updated cancer incidence:* Periodic reporting on the radiation risks of cancer incidence is an important task for the department. A comprehensive analysis to update radiation risk estimates for cancer incidence through 2009 has been completed using updated individual doses and information on lifestyle factors such as smoking in collaboration with the US National Cancer Institute. In addition to the papers on all solid cancer and lung cancer that were published in 2017, a paper for the breast was published (Brenner AV, et al.) in 2018 and another paper for the uterus is in press (Utada M, et al.), and a paper for the colon and rectum has been submitted to an international journal, and a number of papers on individual tumor sites will follow and focus on the shape of the dose-response curves, low-dose risk and risks among those young at exposure, while adjusting for relevant life-style factors (Brenner AV, et al. *Radiat Res* 2018;190: 433–444; Utada M, et al. *JNCI Cancer Spectr* 2019;2(4):pky081; Sugiyama H, et al. *Int J Cancer* 2019;doi: 10.1002/ijc.32275). A paper investigating the origin of curvature in the male dose-response shape was submitted to an international journal by Dr. Cologne of the Statistics Department.
- *Update of individual radiation dose:* Information that is needed to update individual dose of parents of the F<sub>1</sub> cohort members to DS02R1 is being computerized at the Master File section in collaboration with the Department of Statistics.
- *Site-specific cancer studies with histological reviews in the LSS cohort:* The department has a long history of performing joint studies in collaboration with the US National Cancer Institute. These studies attempt to study specific cancers in detail. We currently have a number of studies active, specifically:
  - *Genomic study of thyroid cancer:* A pilot study of whole exome sequence and RNA sequence of papillary adenocarcinoma of the thyroid using formalin-fixed paraffin-embedded tissue samples is underway in collaboration with the US National Cancer Institute and RIKEN of Japan as well as local hospitals in which those samples have been stored. As quality of extracted DNA/RNA from old samples was limited, it was difficult to analyze fusion genes and other structural variations that may indicate somatic mutations/gene alterations due to radiation exposure.
  - *Breast cancer:* Since breast cancer is one of the most radiosensitive tumor sites, we aim to learn more about its radiation pathogenesis. We identified about 1,600 histologically confirmed female breast cancer cases. Of them, about 1,300 ‘intrinsic subtypes’ of estrogen and progesterone receptors and HER2 were determined and radiation risk analysis is underway. In a separate nested case-control study of postmenopausal breast cancer, a paper exploring the joint effects of radiation exposure and endogenous hormone levels was published (Grant EJ, et al. *Int J Radiat Biol* 2018;94:97-105). Data are also being analyzed collaboratively in pooled studies of breast cancer and serum hormone biomarker levels at Oxford University and for premenopausal breast cancer and selected lifestyle factors at the Institute of Cancer Research, UK.

- *Uterine corpus cancer*: As radiation risk of corpus cancer was indicated in the LSS, we continue histological review by a panel of pathologists of about 400 possible cases diagnosed until 2011.
- *Malignant lymphoma*: Histological review has identified about 480 cases during 1950–1995. Increased radiation risk was prominent among survivors in Hiroshima and males, and the risks were similar to previous findings.
- *Soft tissue and bone tumors*: Since most data about radiation risk for sarcomas are after high-dose radiotherapy exposures, we are determining whether there is also risk after low-to-moderate doses. A total of about 130 cases during 1957–2003 is being analyzed in collaboration with the US NCI.
- *LSS hematological study*: After a major paper of risk assessment was published in 2013, routine collection of case information is continuing.
- *Medical radiation exposure*: Information on medical radiation exposure collected by a 2008 mail survey was analyzed in relation to direct radiation dose of A-bombs (Sadakane A, et al. *Radiat Res* 2019;191:507–517).

#### ***Radiation and Noncancer Diseases in the LSS***

- As a paper on detailed analysis of mortality risk of heart disease subtypes was published in 2017, the next comprehensive mortality analysis will be planned after completion of site-specific analyses of the current cancer incidence risk analyses.

#### ***In utero and F<sub>1</sub> Cohorts***

- *In utero cohort study*: Those exposed *in utero* comprise a small but important cohort for the effects of radiation exposure. These data are unique, as there is no other extant study of radiation risk in mid-to-late life after *in utero* exposure. Risk analyses are underway using updated individual doses of DS02R1.
- *F<sub>1</sub> cohort study*: Long-term studies of the F<sub>1</sub> cohort provide a framework for studying germline effects of radiation exposure and contributed important unique data as the largest study with such data. After a major paper of mortality risk assessment was published in 2015, routine collection of case information is continuing. Their individual doses are being updated to DS02R1.

#### ***Data Collection and Processing***

- *Mortality surveillance*: A primary responsibility of the department. Mortality follow-up for all cohorts (LSS, F<sub>1</sub>, *in utero*) continues on a 3-year cycle. Mortality data are complete through 2014 and include underlying cause of death as well as associated causes of death. Archiving early-time materials (scanning and digitization) including questionnaires of the major cohorts and other subjects in the early period has been conducted.
- *Hiroshima and Nagasaki tumor/tissue registries*: Case collection by notifications through 2017 is complete through 2014 in both Hiroshima and Nagasaki. Information from death

certificates through 2016 was registered to the National Cancer Center by of the National Cancer Registry system. Annual reports of each registry were released. A paper of characteristics of bone tumors in the tissue registry of Hiroshima was published (Sugiyama H, et al, *JBJS Open Access* 2018:e0064). The cancer incidence information through 2011 in Hiroshima and 2012 in Nagasaki was summarized in the database of the LSS, *in utero*, and F<sub>1</sub> in 2018 (this is a biennial procedure). Hiroshima and Nagasaki cancer registries contribute to the Japanese National Cancer Registry (cases diagnosed in 2016 and thereafter). Cooperative studies with the National Cancer Center of Japan are also being conducted to improve quality of data linkage between cohort studies and cancer registries in the national cancer registry system. A paper of joinpoint analysis of trend of uterine cervical cancer in Japan, US, and Korea was published in collaboration with US National Cancer Institute (Utada M, et al. *Int J Cancer* 2019;144:2144–2152).

- *Pathology studies:* A database that indexes RERF specimens of formalin-fixed paraffin-embedded tissues is being developed for future specimen utilization and storage in the Biosample Research Center of RERF. Preservation and utilization of pathological materials from the A-bomb survivors in Hiroshima and Nagasaki areas continues in collaboration with community hospitals and universities. Expanded collaboration is being organized.

#### ***Collaboration in Research Clusters and with Other Departments and Institutes***

- *Internal collaborations:* Department of Epidemiology provides information on cause of death, cancer incidence, and risk factors on the subjects derived from LSS, *in utero*, and F<sub>1</sub> cohorts to all departments. Department staff are participating in all *Research Clusters* (Cancer, Genetic, Non-cancer) and existent *Working Groups* (F<sub>1</sub> Clinical Study and Cardiovascular) from the viewpoint of epidemiological design and data in RERF. Specific collaborations are:  
*Department of Statistics:* Study-design and data-analysis, evaluation of radiation exposure (including dosimetry system), especially for low-dose levels.  
*Department of Clinical Studies:* F<sub>1</sub> Clinical Study and cardiovascular disease studies.  
*Department of Molecular Bioscience:* Development of an umbrella program project for comprehensive studies on F<sub>1</sub>. Identification and availability of information of ‘trio’ members and F<sub>1</sub> cohort members, and pathological specimens for molecular biology and epidemiology (cancers of the breast and colon).
- *Domestic collaborations:*  
*Universities and Hospitals in Hiroshima and Nagasaki:* Pathological studies including site-specific cancer studies and storage of surgical specimens.  
*Fukushima Medical University:* Health administration and epidemiological studies for the nuclear power plant accident.  
*National Cancer Center of Japan:* Refinement of cancer registry system and meta-analysis of risk factors of cancer.
- *Overseas collaborations:*  
*US National Cancer Institute:* Updated cancer incidence study, site-specific cancer studies,

training of researchers, pooled analyses of cancer risks (brain tumor, biliary tract cancers).

*Oxford University*: Study of breast cancer and endogenous hormones.

*Institute of Cancer Research, UK*: Pooled analysis of premenopausal breast cancer.

*Asia Cohort Consortium (Tokyo University and various international institutes)*: Pooled analysis of risk factors for various cancers in the Asian populations.

*Diet and Bladder Cancer Pooling Project (DBCP) (Maastricht University)*: Pooled analysis of diet and bladder cancer.

*Biliary Tract Cancer Pooling Project (BiTCaPP)*: Pooled analysis of biliary tract cancers (NCI, USA).

*IARC/IACR, LSHTM*: Cancer registries.

### ***Advocacy and Education of Radiation Epidemiology***

- Advocacy and educational activities are required by radiological community.

*International seminar*: Annual seminar course including lectures and drills was conducted in collaboration with Departments of Statistics and Clinical Studies.

*University of Washington*: Partnership program for graduate school students.

*Korea University*: Exchange of scientists and providing lectures for graduate school students, etc.

*Domestic seminar*: Annual seminar for exchange between biologists and epidemiologists.

*Hiroshima University*: Providing teachers for “Phoenix Leader Education Program for Renaissance from Radiation Disaster” and other undergraduate/postgraduate programs.

*Kurume University*: Exchange of human resources for statistical methodology and providing teachers for postgraduate programs.

*International and domestic academic societies for radiology and epidemiology*: Invited lectures and papers for review of epidemiological activities in ABCC-RERF.