
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 (persons exposed as fetuses), and the F₁ 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 27% of the LSS cohort members were still alive at the end of 2015, including 76% of those who were less than 10 years old at the time of bombing (ATB). Moreover, 74% of the *in utero* and 89% of the F₁ cohorts are still alive. Therefore, continued follow-up of these 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 exposed in early childhood or *in utero*. For the F₁ 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 at exposure 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 utilized 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 pertain 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 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).

FY2019 Epidemiology Department Achievements***Radiation and Cancer in the LSS***

- *Updated cancer incidence (RPs 1-75, 18-61)*: 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, in collaboration with Dept. Statistics and the US National Cancer Institute, using updated individual doses and information on lifestyle factors such as smoking. Papers on all solid cancer, lung cancer, breast cancer, and uterus cancer were published in 2018 while papers on colorectal cancer (Sugiyama H, et al. *Int J Cancer* 2019;146:635-645), liver cancer (Sadakane A, et al. *Radiat Res* 2019;192:299-310), upper digestive cancer (Sakata R, et al. *Radiat Res* 2019; 192:331-44), and central nervous system tumors (Brenner A, et al. *Eur J Epidemiol* 2020; doi:10.1007/s10654-019-00599-y) were published. A paper on prostate cancer is being reviewed by an international journal. Papers on ovarian cancer and comparison of cancer incidence and mortality are being drafted. The series of recent papers focused 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. A paper investigating the origin of curvature in the male dose-response for solid cancer incidence was published by Dr. Cologne of Dept. Statistics.

The updated risk estimates for cancer incidence of individual sites with adjustment for lifestyle factors were mostly similar to those previously reported although some variations were observed. Radiosensitive period, i.e., ages at exposure at which radiation risk is high, seems to be related to high activity of tissue stem cells, e.g., association between development of secondary sexual characteristics and radiation risk of breast cancer and uterine corpus cancer. Emerged non-linearity of dose response relationship for various outcomes highly concerns the radiation science community, but the reasons are still under investigation. Since a majority of the subjects who were exposed at young ages are still alive and risk estimates for them are uncertain at this stage, further follow-up will provide more informative characterization of radiation risks.

- *Updated LSS mortality report (RP 1-75)*: Mortality risk due to atomic bomb radiation among survivors is the most important in evaluation of late health effects due to exposure to atomic bomb radiation. It is because vital status and cause of death of cancer and noncancer diseases are the most essential for evaluation of health outcomes in epidemiology. Also information of vital status and cause of death is collected for LSS subjects living over the whole Japan whereas information on cancer incidence is collected from those living in Hiroshima and Nagasaki prefectures. International risk assessment groups refer the results of mortality risk as the primary basis for radiation-risk estimation. Since the first LSS report was published in 1962, the results were published periodically and the latest 14th report was published in 2012 for the follow-up data during 1950-2003. Therefore, it is appropriate to prepare for a new LSS mortality report (15th) as cancer incidence analysis is nearly complete. Preparation has started using the data until 2015, updated dose estimates, and newly available information on lifestyle and residential factors in collaboration with Dept. Statistics.
- *Update of individual radiation dose (RPs 1-75, 2-61, 4-75)*: Information that is needed to update individual dose of parents of the F₁ cohort members to DS02R1 is being

computerized at the Master File section in collaboration with Dept. Statistics.

- *Site-specific cancer studies with histological reviews in the LSS cohort (RP 9-88)*: The department has a long history of performing joint studies in collaboration with the US National Cancer Institute. These studies provide detailed histological diagnoses by the pathologists' panel using surgically resected specimens of LSS subjects which are borrowed from local hospitals. A research contract supporting these studies ended in July, 2019, with the following studies being continued:
 - *Breast cancer (RP 5-08&6-10)*: We evaluated histological diagnosis of about 1600 female breast cancer cases and were able to determine 'intrinsic subtypes' based on estrogen, progesterone, and HER2 receptor expression for about 1400 cases. Radiation risk analysis is underway.
 - *Uterine corpus cancer (RP 1-06)*: We reviewed histological diagnosis of about 350 female uterine corpus cancer cases. Radiation risk analysis is underway.
 - *Malignant lymphoma (RP 3-94)*: Histological review using immunohistochemical staining established diagnosis of about 500 lymphoma cases using detailed criteria of classification. A manuscript is being drafted.
 - *Soft tissue and bone tumors (RP 4-07)*: Tumors of different histological types originating from various sites underwent histological review, but the number of cases was relatively small (about 120). Radiation risk is being analyzed.
- *LSS hematological study (RPs 18-61, 29-60)*: Update of a comprehensive report published in 2013 is being prepared in collaboration with US NCI by the new research contract.
- *Prostate cancer and PSA (RP-S5-19)*: Characterization of prostate cancer detected as a result of the prostate-specific antigen (PSA) testing and evaluation of the association between radiation dose and PSA value are underway in collaboration with US NCI by the new research contract.
- *Medical radiation exposure (RP 1-75)*: A paper evaluating the influence of medical radiation exposure on the risk estimates of atomic bomb radiation in the LSS was published (Sadakane A, et al. *Radiat Res* 2019;191:507-17). There was no substantial impact of diagnostic radiation exposure on radiation risks from atomic bomb exposure.
- *Collaboration in Cancer Research Cluster*:
 - Design molecular epidemiological studies on cancer using available samples from Adult Health Study (AHS) subjects.
 - Provide information on availability of pathological specimens for molecular and epidemiological studies (cancers of the breast and colon).
 - Provide information on vital status, cause of death, cancer incidence, and risk factors on the subjects to all departments.
 - Collaborate on molecular investigation of chronic myeloid leukemia lead by Dept. Clinical Studies (RP-P2-19).

Radiation and Noncancer Diseases in the LSS (RP 1-75)

- Current preparation for new LSS Report (15th) includes radiation risk analyses of noncancer diseases.

- Collaboration in Noncancer Research Cluster:
 - Collaboration in a Working Group on cardiovascular disease with Depts. Clinical Studies and Molecular Biosciences is continuing.
 - Radiation and metabolic diseases (RP 1-15) lead by Dept. Clinical Studies

In utero Cohort

- *In utero cohort study (RPs 2-61, 18-61):* The cohort is small but important and unique, as there is no other extant study of radiation risk in mid-to-late life after *in utero* exposure. A paper on mortality risk has been submitted to RERF internal review. An elevated radiation risk for solid cancer mortality among females was found, but among males was not. Microcephaly, low birth weight, and loss of father were suggested to be mediators of exposure to atomic bomb radiation on noncancer disease death and external causes of death. It is important to consider the mediating effects of those factors.
- *Chromosome aberration (RP-S3-19):* Association between radiation dose and prevalence of chromosome aberration among *in utero* survivors will be re-analyzed by Dept. Statistics.

F₁ Cohort (Genetic Effects)

- *F₁ cohort study (RPs 4-75, 18-61):* Long-term studies of the F₁ cohort provide a framework for studying germline effects of radiation exposure and contribute important data to the largest study of its kind. After a major paper on mortality risk assessment was published in 2015, routine collection of case information is continuing. The individual doses of F₁ cohort members are being updated to DS02R1. As residential information is essential for ascertainment of cancer incidence through the national cancer registry system, the information on participants in the F₁ Offspring Clinical Study (FOCS) has started to be used.
- Collaboration in Genetic Research Cluster:
 - Development of an umbrella program project for comprehensive studies on F₁, including providing identification and availability of information of ‘trio’ members. See the report by Genetic Research Cluster.

Data Collection and Processing

- *Mortality surveillance (RPs 1-75, 2-61, 4-75):* A primary responsibility of the department. Mortality follow-up for all cohorts (LSS, F₁, *in utero*) continues on a 3-year cycle. Mortality data are complete through 2015 and include underlying cause of death as well as associated causes of death. Archiving has been conducted of early-period materials (scanning and digitization) including questionnaires for the major cohorts and other subjects.
- *Hiroshima and Nagasaki tumor/tissue registries (RPs 18-61, 29-60):* Regular activities in national/local cancer registries and tissue registries are continued including publishing annual reports. Cancer incidence information in the resource database of LSS through 2013 in Hiroshima and 2015 in Nagasaki will be updated by March, 2020, from local cancer registries and tissue registries. Population-based information has been analyzed for specific purposes to underpin radiation risk analyses (RP-S2-17).

- *Pathology studies (RPs 5-89, 1-12)*: A database that indexes RERF specimens of formalin-fixed paraffin-embedded tissues is being developed with inventory of the samples for future specimen utilization and storage in the Biosample Research Center of RERF. Preservation and utilization of pathological materials from A-bomb survivors in the Hiroshima and Nagasaki areas continues in collaboration with community hospitals and universities.
- *Security control*: Documents for all procedures entailing management of personal information at all sections of Dept. Epidemiology were prepared and reviewed to secure personal information of study subjects. Organizational, personal, instrumental, and technical safety measures have been implemented. Education of all staff with access to personal information is ongoing.

Outside collaborations

- *International Collaborations for Radiation Research*
 - US National Cancer Institute*: Updated cancer incidence study, site-specific cancer studies, and training of researchers. Pooled analyses of radiation risk of brain tumors (RP-A1-13) and hematopoietic malignancies (RP A1-16 by Dept. Stat). A new research contract including studies of prostate cancer and PSA in AHS, update of hemolymphoid malignancies, skin cancer, and second primary cancer in LSS for the term 2019-2022.
 - Partnership with the University of Washington*: Partnership program for graduate school students in collaboration with Dept. Statistics. See the report of Dept. Statistics.
 - Potential influence of passive smoking on radiation risk for lung cancer (RP-S2-18)
 - Gastrointestinal cancer survival (RP-S5-18)
 - Mediating effects of tobacco use and alcohol consumption on incidence of related solid cancers (RP-S2-19)
 - Helmholts München*: Mechanistic models of radiation-related colon cancer in collaboration with Dept. Statistics (RP-S4-18).
- *International Collaborations for Other Activities*
 - Institute of Cancer Research, UK*: Pooled analysis of premenopausal breast cancer (RP-A2-14).
 - Asia Cohort Consortium (Tokyo University and various international institutes)*: Pooled analysis of risk factors for various cancers in the Asian populations (RP-A3-10).
 - Diet and Bladder Cancer Pooling Project (DBCP) (Maastricht University)*: Pooled analysis of diet and bladder cancer (RP-A5-12).
 - Biliary Tract Cancer Pooling Project (BiTCaPP, US NCI)*: Pooled analysis of biliary tract cancers (RP-A2-13).
 - University of Hawaii Cancer Center*: Type 2 Diabetes, obesity, and breast cancer risk (RP-S1-18).
 - International Agency for Research on Cancer (IARC)/International Association of Cancer Registries (IACR)*: Cancer registries. Providing population-based data for the International Incidence of Childhood Cancer-3.
 - Global Initiative for Cancer Registry Development*: Providing education of quality control for population-based cancer registry.
- *Domestic collaborations*:

Universities and Hospitals in Hiroshima and Nagasaki: Pathological studies including site-specific cancer studies (RP 9-88), storage of surgical specimens (RP 1-12), effects of therapeutic radiation (RP 2-09). Second primary cancer (RP-A2-08).

National Cancer Center of Japan: Meta-analysis of risk factors of cancer (RP-A2-15). Cooperative studies to improve quality of data linkage between cohort studies and cancer registries in the national cancer registry system.

Japanese Association of Cancer Registries: Providing lectures for data quality for population-based cancer registry.

- *Contribution to national and international radiological activities:*
 - International Commission on Radiological Protection (ICRP):* Providing a member of the Committee 1 (radiation effects).
 - United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR):* Providing a lead writer of report on cancer epidemiology and a member of Japanese delegation and Fukushima Follow-up Project.
 - Fukushima Health Management Survey:* Providing a member of advisory committee.

Advocacy and Education in Radiation Epidemiology

- Advocacy and educational activities are required by the radiological community.
 - International seminar:* Annual seminar course including lectures and drills was conducted to foreign junior scientists in collaboration with Departments of Statistics and Clinical Studies.
 - 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.

Development of Departmental Activities

- Regular meetings have been held on Thursday at which department members present and discuss their achievements, ongoing projects, and plans for research with Epi/Stat members and also other scientists in RERF who need to be involved in the themes.
- *Participation in international seminars and other occasions*
 - Training workshop by IACR and Corsican Summer School on Modern Methods in Biostatistics and Epidemiology. Radiation Epidemiology & Dosimetry Course by US NCI.
 - Training seminar by Japanese Epidemiological Association.