FY2020 Overview

RERF aims to characterize and quantify the late health effects of radiation in atomic-bomb survivors and their offspring with a view to contributing to maintenance of the health and welfare of those individuals and to enhancing the health of all humankind. 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 F_1 cohort (offspring conceived after the bombing) is crucial to accomplishing these purposes. Around 26% of the LSS cohort members were still alive at the end of 2016, including 74% of those who were less than 10 years old at the time of bombing (ATB). Moreover, 76% of the *in utero* and 88% of the F_1 cohorts are still alive. Therefore, continued follow-up of these groups for an additional 20 years or more is clearly essential. 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. Analyses of radiation risk for these outcomes have been conducted in collaboration with the Department of Statistics, including the dose-response shape of radiation risk, epidemiological evaluation of other risk factors for confounding or modification of radiation risks and more precise estimation of the magnitude of risk for radiosensitive subgroups such as those who were exposed in early childhood or *in utero*.

It is also important to investigate consistency between epidemiological evidence and biological mechanisms of radiation effects. Histological specimens of cancer cases have been used for patho-epidemiological studies in collaboration with community pathologists who keep those materials and the US National Cancer Institute. Molecular epidemiological analyses using stored biosamples to investigate genetic susceptibility, gene-environmental interactions and somatic mutations in radiation carcinogenesis are being prepared in collaboration with the Departments of Clinical Studies and Molecular Biosciences with a view to domestic and international institutes.

For the F_1 studies we are developing an integrated program in the Genetics Research Cluster. In this program, the Department of Epidemiology will play the role of evaluating the consistency between the results of observed frequency of genomic alterations in germ cells of F_1 subjects and observed phenotypic risk of cancer and noncancer diseases due to parental radiation exposure in the F_1 cohort.

Information of data and achievements from these cohorts have been used in the pooled analyses of radiation risks and other risk factors by domestic and international research groups. Activities on population-based cancer registries in Hiroshima and Nagasaki contribute to domestic and international organizations such as the International Agency for Research on Cancer [IARC]/International Association of Cancer Registries [IACR].

International radiation 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. 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).

FY2020 Achievements

We consider the platform projects (follow-up of LSS, *in utero*, and F_1 cohorts) with active analyses as our highest priority. Those in maintenance phase and analyses of radiation risk using original information, e.g., site-specific cancer studies using primary information on histopathological diagnosis, are in the second line. Others, most of which are data-sharing projects, have less priority. Each department member has balanced work on all of these kinds of projects.

Radiation and Cancer in the LSS

- *Updated cancer incidence:* Periodic reporting on the radiation risks of cancer incidence is the highest prioritized for the department. A comprehensive analysis to update radiation risk estimates for cancer incidence through 2009 has been completed, in collaboration with the Dept. of Statistics and the US National Cancer Institute, using updated individual doses and information on lifestyle factors such as smoking. Papers on all solid cancer, cancers of the lung, breast, uterus, upper digestive system including stomach colon and rectum, liver were published in 2018 and 2019 while papers on colorectal cancer (Sugiyama H, et al. *Int J Cancer* 2020;146:635-645), central nervous system tumors (Brenner A, et al. *Eur J Epidemiol* 2020;35:591-600) and cancers of the prostate (Mabuchi K, et al. *Radiat Res* 2021;195:66-76), ovary (Utada M, et al. *Radiat Res* 2021;195:60-65), and kidney and urinary tract (Grant E, et al. *Radiat Res* 2021, online ahead) were published. Papers on comparison of cancer incidence and mortality (Brenner A, et al.) and summary of those site-specific analyses (Brenner A, et al.) 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. For the reliability of risk estimation, a paper investigating influence of misclassification of liver cancer information was published by Dr. French of the Dept. of 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. The observed 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 members 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:* Analysis of 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 members living over the whole Japan whereas information on cancer incidence is collected from those living in Hiroshima and Nagasaki prefectures. International risk assessment

groups use the results of mortality risk as the primary basis for radiation-risk estimation. Since the first LSS report was published in 1962, the results have been published periodically and the latest 14th report was published in 2012 for the follow-up data during 1950-2003. Preparation for a new LSS mortality report (15th) has started using the data through 2016, updated dose estimates, and newly available information on lifestyle and residential factors in collaboration with the Dept. of Statistics (Sakata R, Ozasa K, et al.).

- *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 provide detailed histological diagnoses by a pathologists' panel using surgically resected specimens of LSS members which are borrowed from local hospitals. A research contract supporting these studies ended in July,2019, with the following studies being continued:
  - *Breast cancer:* 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 (Brenner A, Yonehara S, et al.).
  - *Uterine corpus cancer:* We reviewed histological diagnosis of about 350 female uterine corpus cancer cases. Radiation risk analysis is underway (Utada M, Nishisaka T, et al.).
  - *Malignant lymphoma:* Histological review using immunohistochemical staining established diagnosis of about 500 lymphoma cases using detailed criteria of classification. A manuscript is being reviewed by *Blood* (Sakata R, Fujihara M, et al.).
  - *Soft tissue and bone tumors:* 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 (Cahoon E, Yonehara S, et al.).

- *Studies on the research contract with US NCI for the term of 2019-2021:*
  - *LSS hematological study:* Update of a comprehensive report published in 2013 is being prepared in collaboration with US NCI by the new research contract for 2019-2021 (Sakata R, Mabuchi K, et al.).
  - *Prostate cancer and PSA:* 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 (Utada M, Mabuchi K, Sugiyama H, et al.).
  - *Skin cancer and second primary cancers:* Analyses of skin cancer incidence risk considering sunlight-exposure and other risk factors and risk of second primary cancer are being prepared in collaboration with US NCI by the new research contract (Sugiyama H, Cahoon EK, Mabuchi K, et al.)

- *Mechanistic model analysis:* One of methods that bridges pathological/molecular mechanisms and epidemiological findings is "mechanistic model analysis." The RERF Dept. of Statistics and Helmholts München have conducted the analyses using colon cancer data of the LSS then the Dept. of Epidemiology is providing cancer

incidence information and epidemiological insights (Sugiyama H).

- *Collaboration in Cancer Research Cluster:*
  - Provide the chair of the Research Cluster (Brenner A).
  - Molecular epidemiological analyses using stored biosamples to investigate genetic susceptibility, gene- environmental interactions and somatic mutations in radiation carcinogenesis are being prepared in collaboration with the Departments of Clinical Studies and Molecular Biosciences with a view to collaboration with domestic and international institutes. This includes available samples from Adult Health Study (AHS) participants and pathological specimens stored in RERF and local hospitals. However, it is crucial to solve the ethical issues with the participants and stakeholders (Brenner A, Sugiyama H, Ozasa K).
  - Provide information on cancer and availability of pathological specimens on chronic myeloid leukemia lead by Dr. N Yoshida of the Dept. of Clinical Studies. (Sugiyama H, Brenner A)
  - Provide information on vital status, cause of death, cancer incidence, and risk factors on the subjects to all departments.

Radiation and Noncancer Diseases in the LSS

- Current preparation for new LSS Report (15th) includes radiation risk analyses of noncancer diseases (Sakata R, Ozasa K, et al.).

- *Collaboration in Noncancer Research Cluster:*
  - Radiation and metabolic diseases lead by Dr. Tatsukawa of the Dept. of Clinical Studies: Providing the information of lifestyle factors such as smoking (Sakata R)
  - Planning of a study on radiation and vascular disease lead by Dr. Nakamizo of the Dept. of Clinical Studies: Providing the opinions on evaluation and adjustment of potential bias and confounding (Ozasa K)

In utero Cohort

- *In utero cohort study:* The cohort is small but important and unique then prioritized the highest, as there is no other extant study of radiation risk in mid-to-late life after *in utero* exposure. A paper on mortality risk was accepted by *European Journal of Epidemiology* (Sugiyama H, et al.). 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. This project will be prioritized moderately in the maintenance phase.

- *Chromosome aberration*: Association between radiation dose and prevalence of chromosome aberration among *in utero* survivors was submitted for internal review of the RERF by Dr. Cologne in the Dept. of Statistics. The results were mostly similar to the previous report. Members of the Dept. of Epidemiology provided the information of lifestyle factors and epidemiological insights (Sakata R, Sugiyama H)

F_1 Cohort (Genetic Effects)

- *F_1 cohort study:* Long-term studies of the F_1 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 F_1 Offspring Clinical Study (FOCS) is being collected for use.

- *Collaboration in Genetic Research Cluster:*
  - Development of an umbrella program project for comprehensive studies on F_1, including providing identification and availability of information of 'trio' members. In this program, the Dept. of Epidemiology will play a leadership role of evaluation of consistency between the results of observed frequency of genomic alterations in germ-line cells of F_1 members and observed phenotypic risk of cancer and noncancer diseases due to parental radiation exposure in the F_1 cohort. Dr. Ozasa leads this umbrella program.

Data Collection and Processing

- *Mortality surveillance:* This is a primary responsibility of the department. Mortality follow-up for all cohorts (LSS, F_1, *in utero*) continues on a 3-year cycle. Mortality data are complete through 2016 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 members in preparation of the Research Resource Center (Sakata R).

- *Hiroshima and Nagasaki tumor/tissue registries:* Precise information of cancer incidence and histological diagnosis of cancers is essential for radiation risk analyses of cancer. The Dept. of Epidemiology has a long history of taking care of the local systems of national and local cancer registries and tissue registries in Hiroshima and Nagasaki, including publishing annual reports. Also, the Department is collecting the information regarding the members of all cohorts from those registries. Cancer incidence information of LSS through 2017 in Hiroshima and 2015 in Nagasaki will be obtained by March, 2021, from national/local cancer registries and tissue registries (Sugiyama H). Population-based information has been analyzed for specific purposes to underpin radiation risk analyses (Sugiyama H).

- *Pathology studies:* 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 (Ozasa K).

- *Individual Radiation Dose:* Individual doses were already updated for the LSS

and *in utero* cohorts. Currently information that is needed to update individual dose of parents of the F_1 cohort members to DS02R1 is being computerized at the Master File section in collaboration with the Dept. of Statistics (Sakata R).

- *Research Resource Center (RRC), Biosample Research Center (BRC), and Data Management/Documentation Committee (DMDC):* Documents and biosamples in the Master File Section, Tumor and Tissue Registry Office, and Pathology Laboratory are indexed and digitized in relation to the above centers, and the principles for utilization of those materials are discussed in the committee (Ozasa K, Sakata R, Sugiyama H).

- *Security control:* Documents for all procedures entailing management of personal information at all sections of the Dept. of Epidemiology were prepared and reviewed to secure personal information of study populations. Organizational, personal, instrumental, and technical safety measures have been implemented. Education of all staff with access to personal information is ongoing (Ozasa K, Sakata R, Sugiyama H).

Outside collaborations

- *International Collaborations for Radiation Research*

  US National Cancer Institute: This includes the updated cancer incidence analyses (Page 1), site-specific cancer studies and research contract-based projects (Page 2), training of researchers, and other data-sharing projects including pooled analyses of radiation risk of brain tumors (Sakata R) and hematopoietic malignancies (Ozasa K).

  Partnership with the University of Washington: The Depts. of Epidemiology and Statistics have created a "Radiation Partnership Program" with the University of Washington to mentor and collaborate with graduate school students in epidemiology and biostatistics. The goals have been training in radiation epidemiology and collaborative research projects in biostatistics. The program started in 2017. Since then, six students have been involved in the program and three of them have graduated with an MPH degree. Projects in 2020 are as follows.

  - Potential influence of passive smoking on radiation risk for lung cancer (Sakata R). A paper is under review by an international journal.
  - Gastrointestinal cancer survival (Sugiyama H). A paper by UW student was published (Bockwoldt B, et al. *Cancer Epidmiol Biomarker Prev* 2020, online ahead)
  - Estimation of residual time acceleration of atomic bomb survivors (Sakata)
  - Mediating effects of tobacco use and alcohol consumption on incidence of related solid cancers (Utada M).
  - Female reproductive factors on radiation related lung cancer (Utada M)

  Helmholts München: Mechanistic models of radiation-related colon cancer in collaboration with the Dept. of Statistics (Sugiyama H).

- *International Collaborations for Other Activities*

  Institute of Cancer Research, UK: Pooled analysis of premenopausal breast cancer (Brenner AV).

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

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

Biliary Tract Cancer Pooling Project (BiTCaPP, US NCI): Pooled analysis of biliary tract cancers (Grant EJ).

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 (Sugiyama H).

Global Initiative for Cancer Registry Development: Providing education of quality control for population-based cancer registry (Sugiyama H).

- *Domestic collaborations:*

Universities and Hospitals in Hiroshima and Nagasaki: In addition to the fundamental collaborative activities stated above (Page 4), effects of therapeutic radiation (Sakata R) and second primary cancer (Utada M) are investigated.

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

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

Shizuoka University and Fukuoka Women's University: Weight fluctuation and cancer and cardiovascular disease mortality (Ozasa K).

- *Contribution to national and international radiological activities:*

International Commission on Radiological Protection (ICRP): Providing a member of the Committee 1 (radiation effects) (Ozasa K).

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Providing a lead writer of report on cancer epidemiology (Brenner AV) and a member of Japanese delegation, Fukushima Follow-up Project, and ad hoc Working Group on Effects and Mechanisms (Ozasa K).

Fukushima Health Management Survey: Providing a member of advisory committee (Ozasa K).

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 (suspended in 2020 due to COVID-19).

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

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 (restricted in 2020 due to COVID-19).

The 3rd Beebe Seminar (webinar): Commemorating the 75th Anniversary of the Atomic Bombings Studies on 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*
  In-person programs were restricted in 2020 due to COVID-19, but many online programs were available instead.