

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 F₁ cohort (offspring conceived after the bombing) is crucial to accomplishing these purposes. Around 23% of the LSS cohort members were still alive at the end of 2017, including 71% of those who were less than 10 years old at the time of bombing (ATB). Moreover, 75% of the *in utero* and 87% of the F₁ 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*.

For the F₁ studies we are developing an integrated institution-wide program in the Hereditary Genetics Research. In this program, the Department of Epidemiology will play the role of evaluating the relationship between the results of observed frequency of genomic alterations in germ cells of F₁ subjects and observed phenotypic risk of cancer and noncancer diseases due to parental radiation exposure in the F₁ 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).

It is also important to investigate the mechanistic basis for epidemiological results. In this regard, previous have used histological specimens of cancer cases for patho-epidemiological studies in collaboration with community pathologists, who keep those materials, and the US National Cancer Institute. Further, a RERF-wide interdisciplinary molecular epidemiological initiative using stored biosamples to investigate genetic susceptibility, gene-environmental interactions and somatic mutations in radiation carcinogenesis is currently being developed. Such a program will involve interdisciplinary research across all RERF departments as well as promote domestic and international collaborations.

FY2022 Epidemiology Department Achievements

We consider the platform projects (follow-up of LSS, *in utero*, and F₁ 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 and by the sites planned (lung, breast, uterus, upper digestive system including stomach colon and rectum, liver, colon, rectum and central nervous system, prostate, ovary, and kidney and urinary tract) were published through 2021. A paper on comparison of cancer incidence and mortality (Brenner A, et al. *Radiat Res* 2022;197:491-508) was published. A summary paper on those site-specific analyses (Brenner A, et al.) are being prepared. 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. 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. The observed non-linearity of dose response relationship for various outcomes highly concerns the radiation science community, but the reasons are so complicated as indicated in the latest paper by Brenner, *et al.* 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:* 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 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 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. Analysis for a new LSS mortality report (15th) has started using the data through 2017, updated dose estimates, and newly available information on lifestyle and residential factors in collaboration with the Dept. of Statistics. These analyses include investigation of dose-

response shape and radiation risk at low dose levels considering potential confounding by geospatial factors, lifestyle factors (smoking, alcohol drinking, body mass index), some indicators representing socioeconomic status, and so on, and also variation in baseline rates. Analysis of the same models that were used in the LSS 14 Report has been conducted for the data extended to 2017, and the results were substantially similar to the previous report. An integrated lifestyle dataset including information obtained from the Mail Survey 2008 has been prepared. Currently, analysis is continued using the parametric background model used in our cancer incidence studies (Sakata R, 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 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:* 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. Paper is being prepared (Brenner A, Yonehara S, et al.).
 - *Uterine corpus cancer:* We reviewed histological diagnosis of about 300 female uterine corpus cancer cases. Radiation risk analysis is underway (Utada M, Nishisaka T, et al.).
 - *Malignant lymphoma:* Following the paper for lymphoma cases reviewed by pathologists, a paper for multiple myeloma was submitted to an international Journal (Yoshida N, Sakata R, et al.).
 - *Soft tissue and bone tumors:* Tumors of different histological types originating from various sites (upper or lower extremities, trunk, etc.) 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 by Hsu et. al. in 2013 is being prepared in collaboration with US NCI (Sakata R, Mabuchi K, et al.).
 - *Prostate cancer and PSA:* A paper on positive dose-response of prostate cancer with little bias caused by the prostate-specific antigen (PSA) testing in AHS examination has been submitted to *Radiat Res* in collaboration with US NCI (Utada M, Mabuchi K, Sugiyama H, et al.).
 - *Skin cancer and second primary cancers:* Datasets for analyses of skin cancer incidence risk considering sunlight-exposure and other risk factors, and risk of second primary cancer were completed in collaboration with US NCI (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 Helmholtz München have conducted analyses using colon cancer data of the LSS (RP by Dept. Stat.). 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).
 - A molecular epidemiological initiative across RERF using stored biosamples to investigate genetic susceptibility, gene-environmental interactions and somatic mutations in radiation carcinogenesis is being developed. This includes available samples from Adult Health Study (AHS) subjects and pathological specimens stored in RERF and local hospitals. Identification of sample within RERF is currently underway. The availability of sample from local hospital is more complicated. To facilitate the evaluation and utilization of stored specimens in RERF, Dr. Tsuruyama of the Dept. of Molecular Biosciences has been appointed as a concurrent research scientist (Brenner A, Sugiyama H).
 - 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, 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)
 - Radiation and incidence of myocardial infarction lead by Dr. Kurisu of the Dept. of Clinical Studies: Providing epidemiological advice in the study design phase (Sakata R, Kadowaki Y)

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 published (Sugiyama H, et al. *Eur J Epidemiol* 2021;35:415-428). Currently this project is prioritized moderately in the maintenance phase.
- *Chromosome aberration (RP by Dept. Stat.):* Association between radiation dose and prevalence of chromosome aberration among *in utero* survivors was published 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).

F₁ Cohort (Genetic Effects)

- *F₁ cohort study*: 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 the parents of F₁ cohort members will be updated to DS02R1 by March, 2023 and the location at the time of bombing for the parents whose exposure status was unknown were investigated in the basic survey materials and updated (Sakata R). 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 been collected and the record linkage will conduct (Sugiyama H, Kadowaki Y).
- *Collaboration in Genetic Research Cluster*:
 - An umbrella program project for comprehensive studies on F₁, including providing identification and availability of information of ‘trio’ members has been developed. In this program, the Dept. of Epidemiology will play a leadership role in a genotype/phenotype analyses. Dr. Noda of the Dept. of Molecular Biosciences 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, F₁, *in utero*) continues on a 3-year cycle. Mortality data are complete through 2017 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 as part of the developing 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 communication with local community, publishing annual reports, and contribution to the related committee to establish the basic plan for cancer control in each municipality. Also, the Department is collecting the information regarding the members of all cohorts from those registries. Since the legal system of national cancer registry is active for cancer cases diagnosed in 2016 or later, the department staff has made huge efforts to utilize the information for studies in RERF. Although there are practical problems due to the legal restrictions such as strict safety control standards of facilities, unlinkable anonymization in analytical datasets, and discarding the datasets after completion of the study, the safety control organizationally, physically, technically, and educationally has been completed for the cancer information users in RERF. The infrastructure for the users in RERF has been arranged (e.g., construction of office door locks, restriction of PC for analysis, internal web page for providing information on how to use the cancer incidence data for research, data dictionary, and application to make the dataset linked with cancer incidence data). The webinar introduced the related-law and regulations that users must follow and the new infrastructure in RERF. However, no transfer of the data linked with the National Cancer

Registry data to foreign countries is not allowed. We must overcome this problem together with epidemiologists and outside RERF researchers to share RERF cancer incidence data for collaborative studies. Tissue registry in Hiroshima was ceased in 2021, so we are planning alternative methods to collect the information of histological materials of LSS subjects with local pathologists in Hiroshima. Tissue registry in Nagasaki is continued and the information is continuously available for us. Cancer incidence information of LSS through 2019 in both Hiroshima and Nagasaki will be obtained by March 2023, from the National Cancer Registry (Sugiyama H). Population-based information has been analyzed for specific purposes to underpin radiation risk analyses and has been submitted to the worldwide summary program, the Cancer Incidence in Five Continents, XII, by the International Agency for Research on Cancer (IARC)/International Association of Cancer Registries (IACR). In addition, the cancer information is planned to contribute on CONCORD-4 study by the London School of Hygiene & Tropical Medicine (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 (Sakata R).
- *Individual Radiation Dose:* Individual doses were already updated to DS02R1 for the LSS and *in utero* cohorts, and will be updated for the parents of F₁ cohort members by March 2023 in collaboration with the Dept. of Statistics (Sakata R).
- *Research Resource Center (RRC) and Biosample Research Center (BRC):* 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 (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 subjects. Organizational, personal, instrumental, and technical safety measures have been implemented. Education of all staff with access to personal information is ongoing (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).
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 2021 are as follows.

- Estimation of residual time acceleration of atomic bomb survivors (RP by Dept. Stat., 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 (Brenner AV) A paper is being reviewed by Radiation Research.

Helmholts München: Mechanistic models of radiation-related colon cancer in collaboration with the Dept. of Statistics (RP by Dept. Stat., 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 Cancer Incidence in Five Continents, XII (Sugiyama H). A representative from Asia of IACR. (Sugiyama H)

- *Domestic collaborations:*

Universities and Hospitals in Hiroshima and Nagasaki: Fundamental collaborative activities stated above 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). Rare Cancer

Incidence study based on the population-based cancer registries in Japan (Sugiyama H)

Japanese Association of Cancer Registries: Providing lectures how to contribute the CI5-XII (Sugiyama H).

Shizuoka University and Fukuoka Women's University: Weight fluctuation and cancer and cardiovascular disease mortality (RP by Dept. Stat., Kadowaki Y).

- *Contribution to national and international radiological activities:*

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 (Sakata R).

Fukushima Health Management Survey: Providing a member of advisory committee (Sakata

R).

International Commission on Radiological Protection (ICRP): Providing a member of the Task Group 122 to update detriment calculation for cancer (Brenner A).

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 2021 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 (held by Zoom session in 2022).
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 2021 due to COVID-19).

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 still restricted in 2022 due to COVID-19, but many online programs were available instead.