DEPARTMENT OF EPIDEMIOLOGY

Mission and Specific Objectives

RERF aims to characterize and quantify late health effects of radiation in atomic-bomb survivors and their offspring with the goal of contributing to maintenance of the health and welfare of those individuals and 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 bombings) are crucial for accomplishing these aims. Specifically, the Department:

1. Conducts regular follow-up and analysis of the vital status and causes of death of LSS survivors throughout Japan, and cancer incidence in Hiroshima and Nagasaki prefectures, where a large percentage of the survivors still resides. Analyses of radiation effects on risk for these outcomes are conducted in collaboration with the Department of Statistics, to clarify the dose-response shape, epidemiological evaluation of confounding, modification of radiation risk by other risk factors, and more precise estimation of the magnitude of risk for radiosensitive subgroups such as those who were exposed in early childhood or *in utero*.
2. Has a key role in creating and shaping an integrated, institution-wide research program in molecular epidemiology. Under this program, the Department of Epidemiology, in collaboration with other departments, will conduct interdisciplinary molecular epidemiological studies in collaboration with internal RERF and external researchers to investigate the mechanistic basis underlying epidemiological observations in the survivors and F1 generation.
3. Collaborates on pooled analyses of radiation risks and other risk factors with domestic and international research groups. Data and findings from the LSS and the *in utero* and F_1 cohorts have long been utilized in pooled analyses of radiation risks and other risk factors by domestic and international organizations. Population-based cancer registry data also contribute to world-wide epidemiological cancer incidence/survival studies organized by the International Agency for Research on Cancer (IARC), the International Association of Cancer Registries (IACR), and the London School of Hygiene and Tropical Medicine.

International radiation risk assessment groups continue to use results from the LSS cohort as a foundation for radiation-risk projections due to the unparalleled nature of the data, based on a large cohort of members exposed at all ages, with a wide range of well-characterized doses and long-term, high-quality disease follow-up. Major findings from our studies are utilized extensively for the creation of high-profile reports 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). The Department's Dr. Brenner is a member of an expert group engaged in preparation of the new UNSCEAR report on radiation and cancer, serving as a focal point for contributing the newest results as they arise from the latest RERF cancer incidence studies. Each department member balances work on all of these projects.

Department Resources

Data on Demographics, Lifestyle, Exposure and Mortality of the LSS, In Utero, and F_1 cohorts

LSS cohort: 120,321 cohort members consisting of 93,741 atomic bomb survivors identified through a survey conducted at the time of the 1950 Japanese national census and 26,580 persons who were living in Hiroshima or Nagasaki in the early 1950s, but who were not in either city at the time of bombings.

In Utero cohort: A cohort consisting of 3,636 persons exposed in the mother's womb. This cohort was established on the basis of birth certificates submitted in both cities from the time of the bombings through the end of May 1946.

F1 cohort: A cohort of 76,814 children of survivors who were conceived after parental exposure. Subjects were born between May 1946 and December 1958 identified based on birth certificates submitted in both cities, and children of LSS cohort members who were born between 1959 and 1984.

These data are maintained and updated by obtaining follow-up information by Master File Section of the Department of Epidemiology and stored in the Information Technology Department (ITD) database.

Cancer Incidence Data

Cancer incidence data for members of the major RERF cohorts are routinely obtained from the regional population-based cancer registries in Hiroshima, Nagasaki and the National Cancer Registry in Japan. The Tumor and Tissue Registry Offices of the Department of Epidemiology are responsible for the summary of primary cancers experienced in members of the major cohorts. These cancer incidence data are stored in the ITD resource database. Individual level data are pseudonymized and processed for analysis in the Epidemiology Analysis Office.

Pathological samples

The Pathology Laboratory stores and maintains formalin-fixed, paraffin-embedded tissue blocks, and slide specimens obtained at the time of autopsy, as well as surgical samples collected from city hospitals.

Internal and External Collaboration

Internal collaboration

The Department of Epidemiology provides cohort demographic, risk factor, mortality, and cancer-incidence data to all RERF researchers and performs collaborative research using these data.

External collaboration

- *International Collaboration for Radiation Research*

  U.S. National Cancer Institute: Site-specific cancer studies and research, contract-based projects, and other data-sharing projects including pooled analyses of radiation-related risk of brain tumors (RP-A1-13, RP-S2-20, Sakata R; RP-S1-21, RP-S2-21, Sugiyama H).

  Partnership with the University of Washington:

  - Mediating effects of tobacco use and alcohol consumption on incidence of related solid cancers (RP-S2-19, Utada M).
  - Female reproductive factors and radiation-related lung cancer risk (RP-S1-20, Brenner AV).
  - *Helmholts München:* Mechanistic models of radiation-related colon cancer in collaboration with the Department of Statistics (RP-S4-18, by Stat. Dept., Sugiyama H).

- *International Collaboration for Other Activities*

Institute of Cancer Research, UK: Pooled analysis of premenopausal breast cancer; In analysis (RP-A2-14, Brenner AV).

Diet and Bladder Cancer Pooling Project (DBCP) (Maastricht University): Pooled analysis of diet and bladder cancer (RP-A5- 12, Kadowaki Y).

Biliary Tract Cancer Pooling Project (BiTCaPP, US NCI): Pooled analysis of biliary tract cancers (RERF-provided data were used). (RP-A2-13, Kadowaki Y).

International Agency for Research on Cancer (IARC)/International Association of Cancer Registries (IACR): Cancer registries. Data sharing of regional population-based cancer registry data in Hiroshima and Nagasaki for the Cancer Incidence in Five Continents, XII (Sugiyama H). Serving as a representative of Asia and the Near East region of IACR (RP S2-17, Sugiyama H).

London School of Hygiene and Tropical Medicine:

- Cancer registries. Data sharing of regional population-based cancer registry data in Hiroshima and Nagasaki for the CONCORD-4 study of global surveillance of trends in cancer survival (RP S2-17, Sugiyama H).
- Facilitating the publication of the Japanese CONCORD-3 Monograph based on data from 16 Japanese regional cancer registries participating in CONCORD-3. (RP 4-16, Sugiyama H).

- *Domestic collaboration*

Universities and Hospitals in Hiroshima and Nagasaki: Opportunities for collaborative activities (RP 9-88, RP 1-12) are shared and discussed.

National Cancer Center of Japan:

- Meta-analysis of risk factors of cancer (RP-A2-15, Utada M).
- Rare Cancer Incidence study based on the population-based cancer registries in Japan (RP S2-17, Sugiyama H).
- Research on the development and utilization of statistical information on cancer (RP S2-17, Sugiyama H).
- Poor prognosis cancer statistics (RP-S2-17, Sugiyama H).

Aichi Cancer Center of Japan: Spatial epidemiological big data analysis for cancer control focusing on socio-economic disparities (RP S2-17, Sugiyama H).

Japanese Association of Cancer Registries:

- Coordinating and facilitating the participation of 21 Japanese regional cancer registries in the UK CONCORD-4 study of the global surveillance of trends in cancer survival, including obtaining each local and national government approval. Board member of the JACR (RP S2-17, Sugiyama H).

Shizuoka University and Fukuoka Women's University: Weight fluctuation and cancer and cardiovascular disease mortality (RP S4-19, by Stat. Dept., Kadowaki Y).

Kurume biostatistics center: Examine the impact of left-truncation, competing risk and unobserved heterogeneity on risk analysis of follow-up data for the LSS cohort (RP S1-24, Sakata R, Kadowaki Y).

- *Contribution to national and international radiological activities*

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Serving as a lead writer for the report on cancer epidemiology (Brenner AV) and a member of Japanese delegation (Sakata R).

Fukushima Health Management Survey: Serving as a member of advisory committee (Sakata R).

International Commission on Radiological Protection (ICRP): Serving as a member of Task Group 122 to update detriment calculation for cancer (Brenner AV).

Radiation Effects Foundation, Evaluation of Radiation Epidemiological Surveys and Studies: Member of committee (Sugiyama H).

Outreach activities: Epidemiology workshops for radiation biologists (Epidemiology Dept.), Lectures on radiation effects for researchers and general public (Sakata R, Utada M, Brenner AV), Introduction of the LSS at the Satellite Seminar in English of the annual meeting for the Japanese Epidemiological Association (Utada M).

- *Contribution to international other activities*

CONCORD-Lancet Global Commission on Cancer: Cancer registries. Commission on the global strategy for cancer control. Serving a report as a commissioner (Sugiyama H).

Outreach activities: Lecture on the international collaborative studies using population-based cancer registry data at the international session of the annual meeting of the Japanese Cancer Association (Sugiyama H)

FY2024 Epidemiology Department Highlights

The Department of Epidemiology maintains three major cohort studies for: 1) atomic bomb survivors (LSS), 2) *in utero* survivors, and 3) offspring of survivors (F_1). Around 21% of the LSS cohort members were still alive at the end of 2020 (the most recent date for which we have complete information on vital status), including 67% of those who were less than 10 years old at the time of the bombings (ATB). Moreover, 72% of the *in utero* and 86% of the F_1 cohorts were still alive as of 2020. These cohorts are the basis of the major RERF analyses of radiation-related risk in humans, conducted not only by the studies of the Department of Epidemiology, but by all departments within RERF. Individual radiation doses have been estimated and continuously revised as newer techniques become available, based on the information stored in the Department of Epidemiology.

The cancer incidence study among major cohort members is a platform research project at RERF. The Department of Epidemiology is responsible for obtaining cancer information from the regional cancer registries in Hiroshima and Nagasaki under the National Cancer Registry system. RERF provides subject information to the registries, and the responsible municipalities provide cancer information, linking it to the subjects' identification for RERF. The Tumor and Tissue Registry Offices of the Department of Epidemiology in Hiroshima and Nagasaki have completed the summarization of cancer patient information for those diagnosed during the period 1958–2019. As part of the fourth cycle of the LSS cancer incidence study, which includes an additional 10 years of follow-up from the previous study, a total of 26,360 first primary solid cancers were observed. An additional 3,832 cases (a 17% increase) were identified. The annual number of solid cancer cases increased until 2000, but the number began to decline as the number of surviving subjects decreased. Radiation-associated cancer incidence risk among LSS subjects will be analyzed, incorporating the new organ dose, by all members of the Department of Epidemiology in collaboration with the Department of Statistics.

Following a presentation at the IsoRed conference in 2023, Dr. Brenner conducted additional joint-endpoint analyses of site-specific cancer risks in the LSS using 1958–2009 incidence data (Pierce D, Preston D, *Radiat Res* 1993;134:134-142). The objective was to better understand the sources of all solid cancer dose response curvature among males reported by Grant et al. (Grant et al., *Radiat Res* 2017;187:513-537) and to evaluate heterogeneity of site- specific radiation effects. In these analyses, individual cancer sites were grouped into seven families of physiologically related cancers (upper gastrointestinal, lower gastrointestinal, hepatobiliary, respiratory, urinary, male reproductive, and female reproductive).

Several factors were identified that influenced the dose response curvature for the combined outcome including unaccounted heterogeneity in site-specific baseline rates and models, form of high-dose adjustment, and choice of a representative organ dose for superficially located sites. Under the all solid cancer model and colon dose, the dose response curvature for severalcancer families was steeper than under the preferred cancer-family-specific model and organ dose. These analyses imply that modeling solid cancer as a single outcome by applying a common model and colon dose to all sites combined could bias the dose response estimation. These analyses were conducted in collaboration with the RERF Department of Statistics, Hirosoft, and the U.S. National Cancer Institute.