

## DEPARTMENT OF EPIDEMIOLOGY

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### **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<sub>1</sub> 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 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. Is working towards an integrated, institution-wide research program in molecular epidemiology. Under this program, the Department of Epidemiology will evaluate the relationship between observed frequency of germline genomic alterations and risk of various cancer and noncancer diseases among F<sub>1</sub> individuals due to parental radiation exposure. The Department of Epidemiology is also conducting interdisciplinary molecular epidemiological studies in collaboration with internal RERF and external researchers to investigate the mechanistic basis underlying epidemiological observations.
3. Contributes to pooled analyses of radiation risks and other risk factors by domestic and international research groups. Data and findings from the LSS and the *in utero* and F<sub>1</sub> 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 information as it arises from the latest RERF cancer incidence studies. Each department member balances work on all of these projects.

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### **Department Resources**

#### ***Data on demographics, lifestyle, exposure and mortality of the LSS, In Utero, and F<sub>1</sub> 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 3,638 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.

*F<sub>1</sub> 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 from RERF's Master File Section and stored in the Information Technology Department (ITD) database.

*Accessibility:* The pseudonymized data are stored in a research database that is accessible to all RERF researchers for approved research purposes.

### ***Cancer Incidence Data***

Cancer incidence data for members of the major RERF cohorts are routinely obtained from the population-based cancer registries in Hiroshima and Nagasaki. The RERF Tumor and Tissue Registry Offices 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.

*Accessibility:* The pseudonymized data can be accessed by users approved by relevant local authorities.

### ***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.

*Accessibility:* The specimens can be used for research purposes based on Research Protocols (RPs) approved after reviews by the RERF Institutional Review Board (IRB) and Committee on Biological Samples (CBS). An inventory of pathological specimens is currently being developed.

### **Internal and External Collaboration**

#### ***Internal collaboration***

The Department of Epidemiology provides basic, mortality, and cancer-incidence data of cohorts for all RERF researchers and performs collaborative research using these data.

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### **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). Manuscript under review by *Radiation Research*.

*Helmholts München:* Mechanistic models of radiation-related colon cancer in collaboration with the Dept. of Statistics (RP-S4-18, by Dept. Stat., Sugiyama H).

- *International Collaboration for Other Activities*

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

*Asia Cohort Consortium (Tokyo University and other international institutes):* Pooled analysis of risk factors for various cancers in the Asian populations (RP-A3-10, Sakata R).

*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 (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). One departmental staff representing Asia and the Near East on 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 (RP S2-17, 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). Member of the Task Force for the Restoration of the National Cancer Registry System (Sugiyama H).

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

*Shizuoka University and Fukuoka Women's University:* Weight fluctuation and cancer and

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cardiovascular disease mortality (RP S4-19, by Dept. Stat., 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 the 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).

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### FY2023 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<sub>1</sub>). Around 22% of the LSS cohort members were still alive at the end of 2019, including 69% of those who were less than 10 years old at the time of bombing (ATB). Moreover, 74% of the *in utero* and 87% of the F<sub>1</sub> cohorts were still alive as of 2019. These cohorts are the basis of the major RERF analyses of radiation-related risk in humans, conducted not only by the studies of 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 current update of the exposure information for calculation of DS02R1 doses for F<sub>1</sub> subjects is ongoing with a target completion in 2024. For detailed timelines regarding the next set of analyses of the LSS, In Utero, and F<sub>1</sub> cohorts respectively, please see Figure 1 (LSS) (p11) and RP1-75 (p25), Figure 3 (*In Utero*) (p12) and Figure 4 (F<sub>1</sub>) (p12).

Utada et al. reported that the observed radiation risk for prostate cancer does not change even after consideration of prostate-specific antigen (PSA) testing among the Adult Health Study (AHS) participants. Prostate cancer is one of the few cancer sites for which the relationship with radiation exposure has not been clearly established. The most recent cancer incidence study series reported a significant increased radiation-related risk for prostate cancer (Mabuchi K et al., *Radiat Res* 2021;195:66-76). PSA testing has been widely used for prostate cancer screening since the 1990s and has been offered to the AHS participants since 2004. As the AHS includes more individuals with high dose radiation exposure among LSS subjects, we investigated the potential impact of PSA testing on radiation risk of prostate cancer observed in the latest analysis. We found that although the PSA testing among AHS participants increased baseline prostate cancer incidence rates, it did not impact the estimated radiation risk (Utada M, et al. *Radiat Res* 2023;200:96-101). This study was conducted in collaboration with RERF's Departments of Statistics and Clinical Studies, and the U.S. National Cancer Institute (NCI).

Cancer incidence information for 2014–2017 in Hiroshima Prefecture, as well as in seven prefectures and all of Japan, has been published in the Cancer Incidence in Five Continents, edited by the International Agency for Research on Cancer/International Association of Cancer Registry. This is the first project since 2016 to share individual-level, anonymized cancer registry data with overseas researchers provided by the Japanese National Cancer Registry under the Cancer Registry Promotion Act. It is hoped that the successful shared publication will lead to the promotion of further international collaborative research using cancer registry data in the future. (Sugiyama H, Cancer Incidence in Five Continents, Volume XII. *IARC Scientific Publications* No. 169)