

## DEPARTMENT OF EPIDEMIOLOGY

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, and the F<sub>1</sub> 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 are also collected by tissue registries in collaboration with community pathologists. Around 33% of the LSS cohort members were still alive at the end of 2011, including 81% of those who were less than 10 years old at the time of bombing (ATB). Moreover, 81% of the *in utero* and 90% of the F<sub>1</sub> cohorts are still alive. Therefore, continued follow-up of these young age 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 in early childhood or *in utero* at the time of exposure.

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 who have had a wide range of well characterized doses and a long-term, high-quality disease follow-up. The LSS mortality and incidence data have been periodically analyzed and a major update to our cancer incidence results through 2009 with updated individual radiation doses will be published in 2016. A comprehensive report presenting a lack of evidence of increased mortality associated with parental radiation exposure among the survivors' children was published in 2015. Major results from our studies are heavily relied upon 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 have pertained 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 only 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 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).

## DEPARTMENT OF EPIDEMIOLOGY

### Departmental Achievements

Page 2

---

### FY2015 Epidemiology Department Achievements

#### *Radiation and Cancer in the LSS*

- *Updated cancer incidence:* 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 using updated individual doses and information of lifestyle factors such as smoking in collaboration with the US National Cancer Institute and a paper on all solid cancer was submitted for internal review and a number of papers on individual tumor sites will follow it. They focus on the shape of the dose-response curves, low-dose risk, and risks among those young at exposure.
- *Update of individual radiation dose:* Information that is needed to update individual dose of the *in utero* and F<sub>1</sub> cohort members is being computerized in the Master File Section in collaboration with the Department of Statistics and Dosimetry Working Group.
- *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 attempt to study specific cancers in detail. We currently have a number of studies active, specifically:
  - *Genomic study of thyroid cancer:* Somatic mutations/genetic alterations that increase susceptibility to radiation-induced thyroid cancer and improve our understanding of radiation-induced carcinogenesis are of great interest because thyroid cancer has been the key disease risk for both Chernobyl and Fukushima. Therefore, a genomic study of papillary adenocarcinoma of the thyroid is being planned in collaboration with the US National Cancer Institute and RIKEN of Japan. As DNA/RNA extracted from old formalin-fixed paraffin-embedded tissue samples creates challenges for sequencing due to fragmented, we are investigating the most efficient methods to extract DNA/RNA.
  - *Breast cancer:* Since breast cancer is one of the most radiosensitive tumor sites, we aim to learn more about the radiation pathogenesis of it. We identified about 1,600 histologically confirmed female breast cancer cases. Among them, about 1,300 cases were available for immunohistochemical staining of 'intrinsic subtypes' with respect to estrogen and progesterone receptors and HER2 and the diagnosis of subtypes is almost completed. In a nested case-control study of postmenopausal breast cancer, the paper exploring the joint effects of radiation exposure and endogenous hormone levels is being revised to re-submit to an international journal. Data are also being analyzed collaboratively in pooled studies of breast cancer and serum hormone biomarker levels at Oxford University and of premenopausal breast cancer and selected lifestyle factors at the Institute of Cancer Research, UK.
  - *Uterine cancer:* The publication of tumor incidence through 1998 (Preston et al., 2007) for the first time suggested a radiation dose response for uterine cancer, so we are studying it in more depth. We started histological review by the pathologist panel for about 380 provable cases. Since cancer registry information through 2011 has become available, we will add approximately 90 cases diagnosed between 2004 and 2011.

We need to reconsider the procedures of collecting pathological samples from collaborating hospitals due to the update of Japanese ethical guidelines in April, 2015.

- *Malignant lymphoma*: The tumor incidence data have suggested an association with radiation for men but not for women, but which subtypes and whether other factors may account for this are unknown, so a detailed study has been mounted. Histological review has identified about 480 cases during 1950–1995. A paper of analyses of radiation risks and characteristics of about 480 cases of which subtypes were immunohistochemically diagnosed is being drafted.
- *Soft tissue and bone tumors*: Since most data about radiation risk for sarcomas are after high-dose radiotherapy exposures, we are determining whether there is also risk after low-to-moderate doses. A total of about 130 cases during 1957–2003 is being analyzed in collaboration with the US NCI.
- *LSS hematological study*: After a major paper of risk assessment was published in 2013, routine collection of case information is continuing.
- *Fallout rain exposure*: Reported exposure to fallout rain was obtained from early ABCC questionnaires. Because of public concerns, especially after the Fukushima accident, the data have been analyzed. A paper on analysis of fallout rain exposure and reported acute symptoms (e.g., epilation and petechiae) is being revised for an international journal.

#### ***Radiation and Noncancer Diseases in the LSS***

- *Heart diseases*: Partly because of our recent publication (Shimizu et al., 2010) on radiation dose and heart diseases through 2003, great interest is being shown in the radiation risk of cardiovascular diseases. A paper on detailed analysis of mortality risk and dose response of heart disease subtypes in separate observation periods from 1950 to 2008 was submitted for internal review in collaboration with the Cardiovascular Disease Working Group and Department of Clinical Studies. A linear dose response was significant for valvular heart disease, hypertensive heart disease, and heart failure, but no models were significant for ischemic heart disease.
- *Co-morbidity and noncancer diseases*: Influences of co-morbidity from cancer and various noncancer diseases on risks of mortality after radiation exposure are being examined in collaboration with Kurume University. Radiation risk of mortality of circulatory disease increased with co-morbidity of cancer, but did not increase with other major disease classes. A paper was submitted to an international journal.

#### ***In utero and F<sub>1</sub> Cohorts***

- *In utero cohort study*: Those exposed *in utero* comprise a small but important cohort for the effects of radiation exposure. These data are unique, as there is no other extant study of radiation risk in mid-to-late life after *in utero* exposure. An analysis of cancer and noncancer mortality risks for 1950–2008 has been completed and a paper is in preparation.

## DEPARTMENT OF EPIDEMIOLOGY

### Departmental Achievements

Page 4

- *F<sub>1</sub> cohort study*: Long-term studies of the F<sub>1</sub> cohort provide a framework for studying germline effects of radiation exposure and provide unique data as the only study with such data. A paper on cancer and noncancer mortality risks during 1946–2009 was published (Grant et al., *Lancet Oncol* 2015; 16:1326-23). A paper describing the results from the F<sub>1</sub> Mail Survey was submitted to an international journal.

### **Data Collection and Processing**

- *Mortality surveillance*: A primary responsibility of the department. Mortality follow-up for all cohorts (LSS, F<sub>1</sub>, *in utero*) continues on a 3-year cycle. Mortality data are complete through 2011 and include underlying cause of death as well as associated causes of death. Archiving early-time materials (scanning and digitization) including questionnaires of the major cohorts and other subjects in the early period has been conducted.
- *LSS mail survey*: Data for general use were made available on the RERF database.
- *Hiroshima and Nagasaki tumor/tissue registries*: Case collection by notifications and death certificates is complete through 2013 in both Hiroshima and Nagasaki. Case abstraction from medical records has been completed through 2012 in Hiroshima and through 2014 in Nagasaki, and the abstraction of more recent cases is underway. The cancer incidence information through 2011 in Hiroshima and 2012 in Nagasaki has been cross-checked with the database of the LSS, *in utero*, and F<sub>1</sub>, and summarized. Annual reports of each registry were released. The recent data were provided to the Cancer Incidence in Five Continents, Vol. XI, and the International Incidence of Childhood Cancer, Vol. III, by the International Agency for Research on Cancer. As National Cancer Registry was started in January 2016 based on the Japanese Cancer Registry Law, both Hiroshima and Nagasaki Cancer Registries have prepared for compliance with the new registry system. Cooperative studies with the National Cancer Center of Japan are also being conducted to refine the connection between current local systems and nationwide system.
- *Pathology studies*: A database that indexes RERF specimens of formalin-fixed paraffin-embedded tissues is being developed for future specimen utilization and storage in the Biosample Center of RERF. A system to preserve surgically resected materials from the A-bomb survivors in Hiroshima and Nagasaki areas in collaboration with community hospitals and universities is being organized.

### **Collaboration with Other Departments and Institutes**

- *Internal collaborations*: Department of Epidemiology provides information on cause of death, cancer incidence, and risk factors on the subjects derived from LSS, *in utero*, and F<sub>1</sub> cohorts to all departments. Specific collaborations are:
  - Working groups and projects*: F<sub>1</sub> Clinical Study, cardiovascular diseases, dosimetry system
  - Department of Statistics*: Study-design and data-analysis, evaluation of radiation exposure, especially for low-dose levels
  - Department of Clinical Studies*: A cross-appointment of a researcher, sharing data on disease risk factors from AHS, risk analyses of cardiovascular diseases at low levels of radiation exposure.

*Department of Molecular Bioscience:* Identification and availability of information of ‘trio’ members and F<sub>1</sub> cohort members, and pathological specimens for molecular biology and epidemiology (thymus and cancers of the breast, thyroid, and colon)

• *Domestic collaborations:*

*Universities and Hospitals in Hiroshima and Nagasaki:* Pathological studies including site-specific cancer studies and storage of surgical specimens

*Fukushima Medical University:* Health administration and epidemiological studies for the nuclear power plant accident

*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 visiting students and providing teachers for postgraduate programs

*National Cancer Center of Japan:* Refinement of the cancer registry system and meta-analysis of risk factors of cancer

• *Overseas collaborations:*

*US National Cancer Institute:* Updated cancer incidence study, site-specific cancer studies, training of researchers, pooled analyses of cancer risks (thyroid, brain tumor, biliary tract cancers)

*Oxford University:* Study of breast cancer and endogenous hormones

*Institute of Cancer Research, UK:* Pooled analysis of premenopausal breast cancer

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

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

*Biliary Tract Cancer Pooling Project (BiTCaPP):* Pooled analysis of biliary tract cancers (NCI, USA)

*IARC/IACR:* Cancer registries