DEPARTMENT OF CLINICAL STUDIES

The Department of Clinical Studies conducts health-examination programs of the Adult Health Study (AHS) and the F_1 (children of the atomic bomb survivors) Clinical Study. These studies provide the opportunity for a number of specific investigations within RERF and in collaboration with external investigators to be conducted into a variety of health outcomes and the understanding of mechanisms.

The AHS biennial health examinations were initiated in 1958 and continue today. The AHS cohort consists of a subcohort of the Life Span Study (LSS) A-bomb survivors of all ages at exposure, also including those exposed *in utero*. These health examinations represent the only point of regular direct contact with the survivors and provide health benefits to that population through early disease detection. As stated above, such examinations function as the principal source of biological materials that make possible a wide variety of valuable studies by numerous RERF departments and outside investigators. Sera, blood cells and plasma, and urine have been longitudinally collected from the AHS participants and stored since 1969, 1990, and 1999, respectively based on newly obtained informed consent. The AHS program has greatly contributed to RERF's mission of 1) assessing noncancer disease risks from radiation, 2) determining radiation effects on physiological or biochemical abnormalities and correlating this information with other life experiences and modes and patterns of disease, and 3) elucidating mechanisms of radiation effects on cancer and noncancer diseases using stored biosamples and clinical, physiological, and epidemiological information that were obtained through the health examinations.

The AHS continually increases in importance as a result of the accumulation of a large body of clinical and epidemiological data from the 29 rounds of biennial health examinations carried out to date. The AHS have provided the strongest available data to analyze about radiation-related increases in morbidity at low-to-moderate doses for noncancer diseases, such as cardiovascular disease (CVD), hyperparathyroidism, thyroid disease, chronic hepatitis B virus infection, and cataracts, plus subclinical risk indicators and conditions such as inflammation or insulin resistance.

In 2002, the Department of Clinical Studies began the program of F_1 Clinical Study examinations, which were conducted for about 12,000 individuals to analyze the potential heritable effect(s) of A-bomb exposure on polygenic, multifactorial diseases

(e.g., diabetes, hypertension, dyslipidemia, coronary heart disease, and stroke) based on prevalence data obtained from 2002 to 2006. However, owing to the young age of the F_1 group (mean age of about 49 years at that time), most of their disease experience was still ahead. Therefore we converted the sample to a cohort for prospective follow-up and started health examinations every 4 years in November 2010. We have completed the second round of examinations and started the third round.

Epidemiological studies of health effects in Fukushima emergency workers (Nuclear Emergency Workers Study: NEWS) was initiated in 2014. An office of the NEWS was placed within the Department of Clinical Studies, Hiroshima in 2015. Various experiences derived from health-examination programs of the AHS or the F_1 Clinical Study have been used in the longitudinal health study of NEWS.

FY2016 Clinical Studies Department Achievements

Radiation and Cancer

- Completed a reanalysis examining the joint effects of radiation and chronic gastritis by pathological types upon gastric cancer risk and submitted a manuscript for internal review.
- Worked on investigating the pathogenesis of radiation-associated HCC by identifying measured markers that form clusters of chronic inflammation, insulin resistance, and liver fibrosis, and by examining possible radiation-HCC mediation by HBV in collaboration with the Statistics Department. New multidisciplinary project has been developed by involving researchers from Department of Statistics.

Radiation and Noncancer Condition: Cataract

Radiation effects on posterior sub-capsular opacity have been well documented among A-bomb survivors and other exposed population. With regard to radiation effects on cortical/ nuclear opacities, however, evidence appears to be insufficient and study results are inconsistent. Therefore, we have developed new ophthalmological study to obtain lens images by 3 devices; slit-lamp, retro-illumination camera, Scheimpflug camera with standardized method to evaluate the grade of posterior sub-capsular, cortical, and nuclear opacities.

- Started full-scale ophthalmologic examinations for a cataract study in Hiroshima and Nagasaki in April 2016 in collaboration with ophthalmologists in Hiroshima and Nagasaki Universities. Supervision for this study is made by a cataract specialist and scoring of cataract severity will be made by the same person using photographed images.

Radiation and Noncancer Condition: Cardiovascular Disease

It has been recognized since the 1960s that the heart may be damaged by substantial doses of radiation (> 30 Gy), such as doses used during mantle radiotherapy for Hodgkin lymphoma. With regard to lower dose radiation, epidemiological data are insufficient and biologically plausible mechanisms are lacking, although there are several theories which may be applied to lower dose exposure, including microvasculature effects, oxidation, inflammation, and mutation theories. With regard to the implication of lower dose studies, risks of cardiovascular disease (CVD) from exposure to lower dose has a large impact both on public health and patient care, because there are large number of patients and radiation workers exposed to this level of radiation. RERF is in the unique situation in studying non-cancer effects because the large amount of information on non-cancer diseases is available and multidisciplinary approach including epidemiological, clinical and basic studies can be applied.

- Although the LSS study and other studies in the literature have recently identified radiation risks for CVD at low-to-moderate doses, the etiological and pathogenic pathways are not well characterized. Started data analysis examining physiological indices of arteriosclerosis and potential related biomarkers with radiation dose in the AHS.
- The LSS and certain other studies have suggested that heart failure and valvular disease, in addition to ischemic heart disease, are associated with radiation exposure. Continued a study to obtain early indicators of these types of disease, using echocardiography and relevant biomarkers to confirm and elucidate these disease risks in the AHS.

- Completed data collection for CVD incidence study using consistent criteria over the study period since AHS had started, especially for ischemic heart disease (IHD) and stroke in the AHS.
- Continued analyses of the association of chronic kidney disease (CKD) and albuminuria with radiation dose.
- Published a first-author paper on prognostic significance of premature ventricular contractions by electrocardiography (*Ann Noninvasive Electorcardiol*, 2016; 21: 142-51). Started analysis about radiation dose and atrial fibrillation (AF), which induces irregular heart rhythm.

Radiation and Noncancer Condition: Others

- According to suggestions made by SAC, we started medical chart review to detect diabetes with standardized criteria in Hiroshima and Nagasaki.
- Submitted a paper of radiation effects on thyroid dysfunction and autoimmune diseases in the AHS subjects exposed at younger ages to the scientific journal. No dose-responses were observed.
- Continued analyses of thyroid diseases in AHS subjects exposed in utero.
- The LSS and AHS data have shown that chronic liver disease and liver cirrhosis are related to radiation dose. Radiation exposure may accelerate the severity of liver fibrosis irrespective of hepatitis virus infection through insulin resistance or inflammation. Continued cleaning a data set which includes measurement of liver stiffness with the elastometer and blood cytokine levels for AHS subjects exposed at younger ages.
- Published first-author paper showing that radiation did not significantly affect cognition's trajectory from 1992 to2011 among atomic bomb survivors exposed at or after adolescence (*Am J Med*, 2016).
- Continued analyses of the association of retinal vessel calibers with the prevalence of glaucoma.

Other Studies on Noncancer Condition

- Started a new RP on the relation between subclinical thyroid disorders and cognitive function and dementia in the large international cohort studies (Thyroid Studies Collaboration).

Genetic Effects

- Almost completed the second round examination of the longitudinal F_1 offspring clinical study (FOCS) that was initiated in November 2010 on a four-year cycle. 10,304 subjects participated and participation rate during this cycle was 78.7% .
- Started to conduct preliminary tabulation of the prevalence and incidence of individual multifactorial disease outcomes among about 10,000 FOCS participants between November 2010 and October 2015.

Nuclear Emergency Workers Study (NEWS)

- Developed a research plan to examine the long-term health effects of radiation on nuclear

emergency workers and conducted mail contact with approximately 20,000 NEWS subjects. Conducted preliminary health examinations on 512 workers in Fukushima and revised study plan based on results from the preliminary survey. Also standardized procedures for health examinations, including informed consent, questionnaire survey, blood and urine collection, transportation of biosamples to RERF and storage, to conduct health examinations by entrusted medical institutions across the country.

- Developed preliminary plans for collaborations with outside collaborators on special clinical studies of thyroid cancer, psychological effect, and cataract.