

## DEPARTMENT OF CLINICAL STUDIES

The Department of Clinical Studies conducts health-examination programs of the Adult Health Study (AHS) and the F<sub>1</sub> (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 their understanding 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 collected from the AHS participants and stored since 1969, 1990, and 1999, respectively. 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 data from the 28 rounds of biennial health examinations carried out to date. The data have provided the strongest available evidence of 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.

More than a decade ago the Department of Clinical Studies began the program of F<sub>1</sub> 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, coronary heart disease, and stroke)

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based on prevalence data obtained from 2002 to 2006. However, owing to the young age of the F<sub>1</sub> 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 almost completed the second round of examinations and started the third round.

Epidemiological study 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<sub>1</sub> Clinical Study will be made use of in the longitudinal health study of NEWS.

### **FY2015 Clinical Studies Department Achievements**

#### **Cancer**

- Completed reanalysis about 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.

#### **Circulatory Disease**

- Although the LSS study and other studies in the literature have recently identified radiation risks for circulatory diseases at low-to-moderate doses, the etiological and pathogenic pathways are not well characterized. Started data analysis about physiological indices of arteriosclerosis and potential related biomarkers in the AHS.
- The LSS and certain other studies have suggested that heart failure and valvular disease, in addition to ischemic 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.
- Started analyses of the association of chronic kidney disease (CKD) and albuminuria with radiation dose.
- Diabetes and dyslipidemia are major risk factors for cardiovascular disease (CVD) and CKD, but the effects of radiation on those conditions are unclear. Recent large-scale cohort studies for childhood cancer survivors revealed late effects on diabetes and dyslipidemia. Started a new RP to examine the dose response for the development of diabetes in Hiroshima and Nagasaki and to evaluate whether the radiation dose response for diabetes is modified by city and age at the timing of A-bomb.
- Published a first-author paper on prognostic significance of premature ventricular contractions by electrocardiography (*Ann Noninvasive Electorcardiol*, 2015 [Epub ahead of print]). A new RP on radiation dose and atrial fibrillation (Af), which induces irregular heart rhythm was approved and started.

#### **Other Noncancer Conditions**

- Published a paper on the association of radiation exposure with the prevalence of age-related macular degeneration (AMD) among AHS subjects (*Invest Ophth Vis Sci*, 2015; 56: 5401-6).
- Continued analyses of the association of retinal vessel calibers with the prevalence of glaucoma.
- Started a new RP on the ophthalmologic study among AHS subjects. Conducted a training session for ophthalmologists and staffs of Clinical Studies Department in Hiroshima and Nagasaki by cataract specialists on how to observe and record findings and how to take retro-illumination (RIL) images with a RIL type camera. Started ophthalmologic

examinations preliminarily in Nagasaki in November 2015.

- Published a first-author paper on the association of radiation dose with the prevalence of thyroid nodules among AHS subjects exposed at younger ages (*JAMA Internal Medicine*, 2015; 175: 228-36).
- Finished analyses of radiation effects on thyroid dysfunction and autoimmune diseases in the AHS subjects exposed at younger ages.
- The LSS and AHS data have suggested 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 such as TNF- $\alpha$ , IL-6, MCP-1, adiponectin, leptin, and IGF-1 for AHS subjects exposed at younger ages.
- Published two first-author papers on the effects of demographic factors and radiation on the age trend of cognitive function between 1992 and 2011 among subjects exposed at  $\geq$  13 years of age (*J Neurol Sci*, 2015; 351: 115-9; *Am J Med*, 2015 [Epub ahead of print]).

#### Genetic Effects

- Almost completed the second round examination of the longitudinal F<sub>1</sub> offspring clinical study (FOCS) cohort that begun in November 2010 on a four-year cycle, and established a participation rate of 78.5% (10,377 subjects).
- Conducted preliminary tabulation of the prevalence and incidence of individual multifactorial disease outcomes among participants during the first three years of the four-year second round, in preparation for future analysis plan.

#### 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 health examinations preliminarily among 512 NEWS participants in Fukushima and revised the research studies 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.
- Performed collaborations with outside collaborators on special clinical studies of thyroid cancer, psychological effect, and cataract.