# DEPARTMENT OF CLINICAL STUDIES

## Mission and Specific Objectives

The Department of Clinical Studies conducts a variety of health-examination and research programs, including the Adult Health Study (AHS) of atomic bomb survivors and the $F_1$ Offspring Clinical Study (FOCS) comprising their children. The department's mission is to provide leadership in clinical medicine and facilitate multidisciplinary research using data and biosamples obtained from AHS and FOCS participants.

The specific objectives of the AHS are:

1) to monitor development of multifactorial diseases based on clinical follow-up of participants,
2) to assess dose-response relationships between radiation and diseases,
3) to identify diseases associated with radiation exposure, and
4) to clarify potential underlying mechanisms of increased risks for such diseases based on use of biosamples received from the study participants.

The AHS continues to increase in importance due to its accumulation of a large body of clinical and epidemiological data from the study's biennial health examinations. AHS provides the strongest data available to analyze radiation-associated 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, in addition to subclinical risk indicators such as inflammation and insulin resistance.

The objectives of the FOCS are:

1) to monitor development of multifactorial diseases based on clinical follow-up,
2) to elucidate association of parental radiation exposure with disease development in their children, and
3) to facilitate multidisciplinary studies aimed at identifying heritable effects of radiation exposure and underlying mechanisms in collaboration with RERF's other research departments.

The FOCS often provides the first available information globally for achieving the aforementioned objectives, against a backdrop of insufficient human data worldwide involving the potential risk of adult-onset multifactorial diseases in children of individuals directly exposed to radiation.

## Department Resources

*Adult Health Study (AHS)*

The AHS cohort, a sub-cohort of the Life Span Study (LSS) population, was established in 1958 with approximately 20,000 individuals including a base cohort of around 5,000 survivors exposed at less than 2,000 m from the hypocenter who exhibited acute symptoms from radiation exposure, and a control population selected on the basis of distance from the hypocenter and lack of acute radiation symptoms (ME200). The cohort was expanded in 1978 with the addition of about 2,400 higher-dose survivors (ME200-1) and all available roughly 1,000 *in utero* exposed survivors (ME200-2). In 2008, the cohort was expanded again with the addition of more than 1,900 individuals exposed at younger ages (< 10 years old at the bombings) (ME200-3). AHS biennial health examinations were initiated in 1958 and are ongoing. Biosamples have been collected from AHS participants and stored since 1969 (serum), 1990 (blood cells), and

1999 (urine), based on informed consent newly obtained from participants at each of those times.

*$F_1$ Offspring Clinical Study (FOCS)*

The FOCS, a sub-cohort of the $F_1$ mortality cohort, was initiated with the rationale that definitive human data can be best obtained through an ongoing high-quality clinical study conducted until the study participants become elderly, a period marked typically by increased multifactorial disease incidence.

From the $F_1$ mortality cohort, which consists of 76,814 individuals, 24,673 individuals stratified on parental radiation dose were selected for a mail survey conducted between 2000 and 2006. Of the 24,673 $F_1$ subjects who were mailed questionnaires at that time, 14,145 individuals indicated willingness to undergo health examinations, resulting in 11,951 participants being examined during the examination period 2002–2006. The initial ('first-round') of FOCS examinations provided no evidence for increased prevalence of adult-onset multifactorial diseases resulting from parental radiation exposure. However, given the relatively young mean age of the $F_1$ group at the time (roughly 49 years), most of their disease experience was considered to lie in the future, and RERF thus converted the prevalence study to an incidence study for prospective follow-up, initiating a program of FOCS health examinations in four-year cycles starting in November 2010 ('second round'). This prospective study cohort consists of 13,100 $F_1$ subjects who responded favorably to the request to participate in health examinations during the period 2000–2008. A 'fourth round' of examinations initiated in November 2018 was almost concluded in FY2022, and the most recent 'fifth round' was initiated in November 2022. Sera, blood cells, plasma, and urine resulting from the examinations have been collected from FOCS participants and stored since 2002 following informed consent obtained from participants.

The AHS and FOCS health examinations represent the only point of regular direct contact with the survivors and their children and provide health benefits to those populations through early disease detection and more. Such examinations function as a principal source of clinical and epidemiological information and biosamples, enabling a variety of valuable studies to be carried out by RERF's research departments as well as by collaborating external investigators.

**Internal and External Collaboration**

Work to attain these objectives is conducted in collaboration with all RERF research departments, namely the Departments of Epidemiology, Statistics, Molecular Biosciences, Information Technology, and the Biosample Research Center as well as in collaboration with external investigators in Japan and overseas.

**Relevance to the RERF Strategic Goals**

We will continue to follow up AHS and FOCS participants with high quality and accuracy. We will collect and curate clinical and epidemiological information, and related biosamples from AHS and FOCS participants, linking them to consent status. In addition, we will collaborate with other RERF departments, national and international universities, and research institutions to elucidate potential underlying mechanisms of increased disease risk. In particular, we will promote new research using next-generation sequencing, proteomics, and machine learning. We will also provide information about our research activities to non-AHS atomic bomb survivors, non-FOCS second-generation atomic bomb survivors, as well as AHS and FOCS participants and their families through open house events, public lectures, and information disclosure on the website.

## FY2023 Departmental Highlights

*[Platform Protocol: Adult Health Study (AHS)]*
One of our main mission goals is to identify noncancer diseases associated with radiation exposure. Updating the AHS report on the incidence of noncancer diseases not only helps to identify new radiation-associated diseases, but also to reevaluate and strengthen previous findings. Preparation of an analysis plan and creation and checking of data sets were carried out to examine the incidence of noncancer disease (Report 9, 1958–2020) among atomic bomb survivors.

*[Platform Protocol: $F_1$ Offspring Clinical Study (FOCS)]*
The initial examination of the FOCS from 2002 to 2006 provided no evidence for an increased prevalence of adult-onset multifactorial diseases due to parental radiation exposure. However, incidence data will have less potential for bias than prevalence data, if a high-quality clinical study is continued until the subjects become elderly, when many multifactorial diseases develop. The analysis plan of the longitudinal study data (2002–2020) has been developed within the interdepartmental FOCS Analysis Working Group. Data have been thoroughly checked, and the final background state transition intensity (hazard) models have been fitted, checked, and decided upon. The risk analysis was initiated.

*[Radiation and Hematological Malignancies: Myelodysplastic Syndrome (MDS)]*
Atomic bomb survivors have a higher risk of hematological malignancies even more than 50 years after radiation exposure. Recent genome analysis showed that blood samples contain several gene mutations that might be observable before clinical diagnosis. We are searching for mutations in stored blood samples of AHS participants who developed MDS using next-generation genome analysis technology.

*[Radiation and Hematological Malignancies: Leukemia]*
A-bomb survivors had a high risk of hematological malignancies shortly after exposure. Little is known about the genomic alterations in these leukemia cases, but the alterations could play critical roles in radiation-induced leukemogenesis. To reveal the genomic landscape of the leukemia cases, we started a pilot study in which we will perform targeted-sequencing analysis using DNA and RNA extracted from formalin-fixed paraffin embedded (FFPE) samples.

*[Radiation and Liver Cancer]*
The established association between radiation exposure and chronic hepatitis B virus (HBV) infection, together with the known roles of both radiation and HBV in risk of hepatocellular carcinoma (HCC) imply that HBV is, by definition, a mediator. However, the extent of mediation has not previously been established. We estimated mediation proportions for HBV and hepatitis C virus (HCV) infection on risk of HCC in a prospective clinical cohort study, and summarized the results in a manuscript.

*[Radiation and Noncancer Condition: Cataract study]*
Radiation effects on posterior subcapsular cataracts (PSC) have been documented among A-bomb survivors and other exposed populations. However, past reports of radiation effects on cortical (COR) and nuclear (NUC) cataracts have been inconsistent, possibly due to inaccurate diagnosis of the outcomes. The present study used appropriate devices and diagnostic criteria to obtain more precise diagnosis. An association between radiation and PSC, COR and NUC was evaluated, and the results were summarized in a manuscript.

*[Radiation and Noncancer Condition: Thyroid study]*
In a previous AHS thyroid study conducted in 2007–2011 (1st cycle), increased risk of thyroid nodules was observed among atomic bomb survivors exposed in childhood, while risks of thyroid dysfunction and autoimmunity were not apparent. Diagnosis of thyroid disorders at the 2nd examination cycle (2018–2022) was almost completed. The 3rd examination cycle has been conducted since August 2022.

*[Radiation and Noncancer Condition: Atherosclerosis study]*
Associations between radiation and atherosclerosis or circulating inflammatory markers have been observed in A-bomb survivors. To evaluate the potential mechanisms of radiation-induced atherosclerosis, we are focusing on possible mediation by 1) clonal hematopoiesis / T-cell aging / inflammation and 2) abnormal vascular repair. Quality assessment of cytokine measurements has been published in an international journal *(Eur J Med Res*, 2024). Statistical analysis of AHS data is underway.

*[Radiation and Noncancer Condition: Diabetes study]*
A recent AHS study suggested a statistically significant association between radiation dose and diabetes incidence, although the results were inconsistent by city and age at exposure. To investigate whether radiation-related diabetes is associated with either insulin resistance or insulin insufficiency and whether the associations are modified by city of exposure, we have conducted a cross-sectional study of AHS participants (younger than 15 years of age at exposure). A manuscript of the results was submitted to an international journal in 2024.

*[Radiation and Noncancer Condition: Cognition study]*
Studies conducted at ABCC/RERF and elsewhere have documented early-life cognitive deficits in relation to in utero and childhood radiation exposures. We found no significant effects of radiation exposure after examining subjective and objective cognitive functions in these survivors as they reached old age. A paper was published on the relationship between subjective cognition and radiation based on the Neurocognitive Questionnaire (NCQ) among survivors exposed in utero (*Radiat Res,* 2023).