DEPARTMENT OF CLINICAL STUDIES

Departmental Overview

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 study 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 study participants.

The AHS continues to increase in importance due to its accumulation of a large body of clinical and epidemiological data resulting from the study's biennial health examinations. The 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 specific 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 2,000m from the hypocenter who exhibited acute symptoms of 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 approximately 2,400 higher-dose survivors (ME200-1) and all available (~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). The AHS biennial health examinations were initiated in 1958 and are ongoing. Biosamples

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have been collected from the 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 typically marked 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 will be concluded within 2025, 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 being 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 Collaborations

Internal Collaborations

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.

External Collaborations

In collaboration with domestic and international universities and research institutions, we have facilitated the implementation of highly specialized studies.

National:

- Hiroshima University: "Ophthalmological study," "Cardiovascular disease study," "Cardiovascular disease risk factor study," "Liver Cancer Study"

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- Nagasaki University: “Ophthalmological study,” “Cardiovascular disease study,” “Thyroid study,” “Hematological malignancy study,” “Cardiovascular disease risk factor study,” “Epidemiological study of health effects in radiation workers”
- Kanazawa Medical University: “Ophthalmological study”
- Kyoto University: “Hematological malignancy study”
- University of Tokyo: “Hematological malignancy study”
- Kurume University: “Hematological malignancy study”
- Kawasaki Medical School: “Cardiovascular disease risk factor study”
- Toho University: “Lifestyle-related diseases such as cardiovascular disease”
- University of Occupational and Environmental Health: “Epidemiological study of Health Effects in Radiation Workers”
- Hiroshima International University: “Atherosclerosis study”
- Yasuda Women’s University: “Atherosclerosis study”
- Tsuchiya Sogo Hospital: “Thyroid study”
- Hiroshima-Nishi Medical Center: “Cardiovascular disease study”
- Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital: “Hematological malignancy study”
- University of Nagasaki: “Cardiovascular disease risk factor study”

International:

Bern University, Switzerland: “Multicenter collaborative projects on thyroid disease”

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Departmental Highlights

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Radiation and Cancer

[Radiation and Hematological Malignancies: Myelodysplastic Syndrome (MDS)]

Atomic bomb survivors have a higher risk of hematological malignancies even now, 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 perform targeted-sequencing analysis using DNA and RNA extracted from formalin-fixed paraffin embedded (FFPE) samples. We need to make several modifications, especially to DNA sequencing, because the amplicon size was smaller than expected. However, we found that RNA sequencing analysis is feasible for the screening of fusion genes and that DNA sequencing for hot-spot mutations is also feasible.

[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 for radiation-associated risk of HCC in a prospective clinical cohort study of 4,345 atomic bomb survivors. We submitted a manuscript reporting the results to an international journal.

Radiation and Non-Cancer Effects

[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. Preliminary analyses for the incidence of noncancer disease (Report 9, 1958–2020) have been conducted using organ dosimetry based on the DS86 phantoms to assess any doses response while assessing the sensitivity of the results to background modeling.

[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 and the characteristics of the population. The present study used appropriate devices and diagnostic criteria to obtain more precise diagnosis. Associations between radiation and subtypes of cataracts (COR, NUC, and PSC), as well as the additional subtypes (vacuoles, retrodots, and waterclefts). We also analyzed considered surgery cases. A manuscript is under internal review.

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[Radiation and Noncancer Condition: Thyroid study]
A previous AHS study conducted in 2007–2011 (1st cycle) reported increased radiation-related risk of thyroid nodules, but not of thyroid dysfunction and autoimmunity. In 2024, diagnosis of thyroid disorders at the 2nd examination cycle (2018–2022) was nearly complete. The 3rd examination cycle and diagnosis have been conducted since August 2022.

Radiation and Molecular Mechanisms of Disease (Human Studies)
[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 (Nakamizo et al. *Eur J Med Res,* 2024) revealed that VEGF-A, osteoprotegerin, and osteopontin have acceptable variations. Statistical analysis of AHS data is ongoing.

[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 impaired pancreatic β-cell insulin secretion or insulin resistance and whether the associations are modified by city of exposure, we have conducted a cross-sectional study of AHS participants. This study investigated 3,152 survivors who were younger than 15 years at exposure. Homeostasis model assessment of β-cell function (HOMA-β) and HOMA of insulin resistance (HOMA-IR) were used as surrogate indices of pancreatic insulin secretion function and insulin resistance, respectively. Radiation dose was significantly and positively associated with the levels of HOMA-β and HOMA-IR in both Hiroshima and Nagasaki. In addition, in the analysis of factors related to visceral fat and insulin resistance other than HOMA-IR, radiation dose was found to be significantly and positively associated with triglycerides and significantly and negatively associated with adiponectin and HDL cholesterol levels. However, city was not a dose modifier of the radiation response on these markers of visceral fat and insulin resistance including HOMA-IR. Although it is possible that insulin resistance was one of the factors contributing to the increased incidence of diabetes associated with radiation in A-bomb survivors, the cause of the difference in the dose response in the incidence of diabetes between cities remained unclear. A manuscript has been published in 2025 (Tatsukawa et al. *J Clin Endocrinol Metab,* 2025).

Transgenerational Effects
[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 (hypertension, hypercholesterolemia, diabetes mellitus, angina pectoris, myocardial infarction and stroke) due to parental radiation exposure. However, longitudinal 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 and initial risk analysis has been conducted. The NIC status for many of the F_1 parents whose DS02R1 dose was unknown has been confirmed. The parental dose data has been updated by changing doses from missing to zero for all FOCS parents whose status has been newly confirmed to be NIC. Following the update of the illness-death risk data, re-analysis has started.