放影研 RERF

Radiation Effects Research Foundation

A Cooperative Japan-US Research Organization

Radiation Effects Research Foundation

50 Years of Progress

50th Anniversary

1975—2025

50th Anniversary
1975—2025

To all who have supported the research of the Radiation Effects Research Foundation

On this occasion of the 50th anniversary of the establishment of the Radiation Effects Research Foundation (RERF), we would like to express our sincerest and most heartfelt appreciation to everyone for their invaluable and unwavering support and cooperation, which have enabled our continued research over the past half-century.

The research conducted to date at RERF has shed light on the health effects of radiation from the atomic bombings in both A-bomb survivors and their children, findings that form the foundation for advancing the health management, medical care, and support services for the survivors. At the same time, RERF's research is recognized globally for the extensiveness of its study populations, the precision of its data, and the comprehensiveness of its follow-up studies and represent the most important source of information for the formulation of radiation protection standards around the world. RERF owes these achievements to the efforts of so many, which have benefited not only the health of A-bomb survivors but also that of people around the world.

Meanwhile, this milestone serves as a reminder that there is still much to discover through RERF's research into radiation's effects on human health. The best way RERF can repay everyone's selfless contributions is to continue our studies into the future.

With a continued commitment to excellence in research, RERF remains dedicated to serving the health and well-being of A-bomb survivors and their children and contributing to the betterment of public health for all humanity.

In closing, we sincerely ask for everyone's continued support and understanding.

June 2025

RERF directors, staff

Chair/Representative Director

Kenji Kamiya

On the occasion of the 80th anniversary of the atomic bombings and the 50th anniversary of the establishment of the Radiation Effects Research Foundation (RERF), I would first like to offer my most sincere thoughts and prayers to those who lost their lives in the atomic bombings. I also want to express my deepest gratitude to the atomic bomb survivors and their families for their selfless and generous cooperation in our research, as well as to the organizations and individuals that have provided their invaluable guidance and support over the years, especially those representing the governments of the United States and Japan. I also wish to renew my expression of heartfelt respect and congratulations to the Japan Confederation of A- and H-Bomb Sufferers Organizations for its untiring contribution to world peace and selection as the recipient of the 2024 Nobel Peace Prize, an achievement that brought great joy to all of us at RERF.

RERF was established in 1975 based on an agreement between the governments of the United States and Japan, following the reorganization of the Atomic Bomb Casualty Commission (ABCC) into a joint U.S.-Japan research institution that would carry on ABCC's research. RERF has consistently pursued research with the support of the U.S. and Japanese governments, producing results that clarify both the general and detailed health effects of atomic bomb radiation. The research results have been used as basic data for the health management of atomic bomb survivors and the promotion of their medical care and welfare. Moreover, RERF research results are highly regarded by international organizations such as the United Nations Scientific Committee on the Effects of Atomic Radiation and have served as the most important foundational findings for establishment of the international system of radiation protection.

At RERF, we are acutely aware that such significant achievements have only been possible thanks to the invaluable and dedicated cooperation of atomic bomb survivors and their children, who have endured indescribable physical and psychological suffering, for which we maintain a sense of deep gratitude as we go about our work of conducting scientific research. I would be grateful for the understanding that, through such international organizations, the dedicated cooperation of the atomic bomb survivors is a significant contribution to the protection of humanity from radiation.

As we approached the milestone of RERF's 50th anniversary, we adopted a vision that would orient our future research activities based on the achievements made thus far. At this juncture, we made the decision to relocate RERF to the Kasumi Campus of Hiroshima University thanks to the understanding and efforts of many involved, with construction of a new research facility now underway.

As we continue our mission of conducting long-term follow-up studies of atomic bomb survivors and their children, RERF remains committed to pressing on with our efforts to build upon our scientific achievements. We hope that the accurate elucidation of atomic bomb radiation effects on human health will lead to wide acceptance of the atomic bomb survivors' wish of "No More Hiroshimas, No More Nagasakis" among people around the world on the way to the establishment of lasting peace, which represents one of RERF's founding principles.

I conclude my remarks with my sincere hope for your continued support and guidance.

Vice Chair/Executive Director

Preetha Rajaraman

Over the past eight decades, the Radiation Effects Research Foundation (RERF) and its predecessor, the Atomic Bomb Casualty Commission (ABCC), have provided critical insights into the long-term health effects of radiation exposure. Key findings, including identification of radiation-related excesses of leukemia, all solid cancers combined, and most individual cancer sites, have informed the health and welfare of the survivors and their families, and form the basis of radiation protection worldwide.

Moving into the next decade, significant questions remain to be answered from continued follow up of RERF's epidemiologic cohorts, including the identification of emerging radiation-related risks of cancer and non-cancer diseases, and more precise characterization of known risks. As radiation protection increasingly considers the possibility of individualized protection, it will be crucial to better understand the shape of dose-response relationships for various diseases, including how these are affected by factors such as age, sex, genetics, and behavior (e.g. use of smoking and alcohol). With rapid advances in technology, RERF's large collection of biological samples places the institution in a unique position to address questions of risk prediction and disease prevention, elucidate genetic and epigenetic mechanisms of radiation-associated disease, and identify potential radiation biomarkers.

RERF's research has been made possible through the cooperation of many atomic bomb survivors and their families, to whom we express our deepest gratitude. Honoring their invaluable partnership, we remain committed to continuing these investigations to benefit the survivors and their families, as well as science and humanity.

Table of Contents of *Our 50 Years of Progress*

RERF's 50 Years of Progress

1945–1948

1945

August

An atomic bomb was dropped on Hiroshima (6 August 1945, 8:15 a.m.).

An atomic bomb was dropped on Nagasaki (9 August 1945, 11:02 a.m.).

September

Japanese medical teams and scientists from the United States established the Joint Commission.

Dr. Tsuzuki

Dr. Oughterson

Dr. Warren

Train equipped with medical examination facilities

1947

March

A portion of the Hiroshima Red Cross Hospital was leased to establish the Atomic Bomb Casualty Commission (ABCC).

1949–1955

1949

March

A major pediatric program commenced in Hiroshima and Kure.

July

A groundbreaking ceremony was held and construction of research facilities commenced at the Hijiyama site.

Construction in progress at Hijiyama

August

The ABCC A-bomb survivor population census started.

November

Nagasaki ABCC was relocated to Nagasaki Prefectural Kyoiku Kaikan.

Nagasaki ABCC relocated to Nagasaki

1950

January

The Leukemia Survey was initiated (for details, refer to page 21).

August

The Adult Medical Survey commenced in Hiroshima and was later extended to Nagasaki.

October

A national survey of A-bomb survivors was conducted as a supplement to the National Census.

November

Construction of new facilities at the Hijiyama site was completed and relocation initiated.

ABCC relocated to Hijiyama

1956–1975

1958

July

The Adult Health Study commenced (refer to page 16).

August

Written agreement was exchanged with JNIH for conduct of the Life Span Study. The basis of a cooperative US-Japan research system was established (refer to page 16).

Written agreement exchanged with JNIH for conduct of the Life Span Study

1966

June

The first ABCC Open House was held in Nagasaki.

First Nagasaki ABCC Open House

1975

February

A team dispatched by NAS visited ABCC, resulting in a report of the Committee for Scientific Review of ABCC (Crow Committee) that recommended research be continued for at least 20 years.

Crow Committee

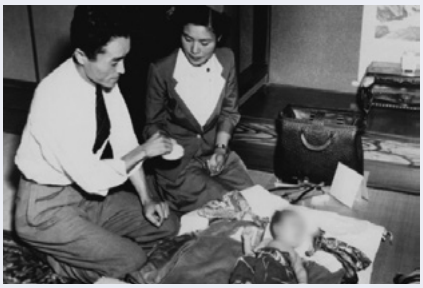
1948

January
The Japanese National Institute of Health (JNIH) of the Ministry of Health and Welfare formally joined the studies of ABCC.

ABCC was relocated to the former Gaisen-kan, Ujina, Hiroshima.

ABCC relocated to Gaisen-kan

March
A major study of birth defects was initiated.



Home visit

July
Nagasaki ABCC was established in Nagasaki Medical University Hospital (Shinkozen Elementary School).

October
A major pediatric program commenced in Nagasaki.

1951

January
A study of children exposed in utero commenced.

1952

January
A pilot study on mortality and cause of death began.

1953

December
A 10-bed ward was established within ABCC facilities in Hiroshima.

1955

September
The first annual Buddhist memorial service was held in Hiroshima honoring autopsied survivors at Tokuo Temple, Tera-machi.

First annual Buddhist memorial service

November
The National Academy of Sciences-National Research Council (NAS-NRC) Ad Hoc Committee reviewed ABCC research design, resulting in recommendations to conduct the "Unified Study Program" based on a fixed population.

The first meeting of the Japanese Advisory Council for ABCC was held in Tokyo.

Seventh meeting of the Japanese Advisory Council for ABCC

1975.04–

April
RERF inauguration ceremonies were held in Hiroshima and Nagasaki.

RERF inauguration ceremony in Hiroshima

Opening ceremony held in Nagasaki

1975–1995

1975

April
The first Board of Directors meeting was held in Hiroshima.

July
The first Scientific Council (present-day Scientific Advisory Committee) meeting was held in Hiroshima.

September
The first meeting of the Hiroshima Local Liaison Council was held.
The first meeting of the Nagasaki Local Liaison Council was held.

First meeting of Hiroshima Local Liaison Council

1977

January
The full-scale Biochemical Genetics Study commenced.

1979

June
RERF was designated as a WHO Collaborating Center.

1982

June
The "A-bomb Radiation Dose Appraisal and Review Committee" was inaugurated.

1983

February
The first US-Japan Joint Workshop for Reassessment of A-bomb Radiation Dosimetry was held in Nagasaki.

1986

April
Chernobyl nuclear power plant accident (RERF began accepting medical professionals and scientists from radiation-affected nations for training).

First US-Japan Joint Workshop for Reassessment of A-bomb Radiation Dosimetry

1996–2005

1996

February
The Blue Ribbon Panel of top scientists was convened to provide recommendations on RERF future research direction for the health study of A-bomb survivors' children and others.

Blue Ribbon Panel

1997

August
The first RERF Open House was held in Nagasaki.

November
The commemorative ceremony and lectures for the 50th anniversary of ABCC-RERF were held in Hiroshima.

50th anniversary of ABCC-RERF

1999

May
An agreement was reached with the Second Generation A-bomb Victims Liaison Council concerning the health study of A-bomb survivors' children.

September
Tokaimura criticality accident.

October
Dispatch of RERF staff for health surveys of residents near Tokaimura.

December
First Scientific Council Meeting was held for Health Effect Study of the Children of A-bomb Survivors.

Agreement reached with Second Generation A-bomb Victims Liaison Council concerning a health study

2006–2011

2006

July
Agreement signed with Hiroshima University on cooperation in education and research.

November
Agreement signed with Nagasaki University on cooperation in education and research.

December
Senior Advisory Committee on the Future Vision of RERF convened; final report submitted in June 2008.

Senior Review Panel

2007

February
Press conference held to announce the results of Health Effects Study of the Children of A-bomb Survivors.

December
Symposium held at NAS to commemorate 60th anniversary of ABCC–RERF establishment.

60th Anniversary Commemorative Symposium held at NAS

2010

July
First meeting held of the Scientific and Ethics Committee for the Clinical Study of the F1 Offspring of A-bomb Survivors (after merger of Scientific Committee, Ethics Committee).

September
First Epidemiological Training Workshop for Radiobiologists held.

November
First RERF Public Lecture held.

1987

July

"US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki" (DS86 final report) was published by RERF.

DS86 final report

September

The final DS86 report was submitted to the ICRP general meeting.

1988

October

Designated a member of WHO Radiation Emergency Medical Preparedness and Assistance Network (REMPAN).

1990

August-September

RERF participated in the IAEA Chernobyl health effects study group.

October

A meeting of the WHO Scientific Advisory Committee on Chernobyl accident was held at RERF.

1995

August

The first RERF Open House in Hiroshima was held.

Crowd at first Hiroshima Open House

October

Sixth WHO REMPAN meeting held at RERF.

November

RERF official website launched.

2000

January

First Ethics Committee meeting held for Health Effect Study of the Children of A-bomb Survivors.

May

Health Effect Study of the Children of A-bomb Survivors began.

2003

March

Final approval was obtained for the new dosimetry system DS02.

Dosimetry system DS02

2005

November

To commemorate the 30th anniversary of RERF, a second-generation A-bombed tree was planted at the Hiroshima Laboratory.

First Council of Radiation Effect Research Organizations held.

Scene of fifth Council meeting held in 2011

December

DS02 report on re-evaluation of atomic bomb radiation doses in Hiroshima and Nagasaki published.

Planting sapling of second-generation A-bombed Chinese parasol tree

2011

March 11

Great East Japan Earthquake.

Fukushima Daiichi Nuclear Power Station accident.

Emergency Medical Response Committee established within RERF.

RERF staff dispatched for radiation dose measurement and radiation-related health consultations for residents in the disaster-affected areas.

Measuring the radiation levels in soil

Presentation of Minister of Health, Labour and Welfare's commendation for RERF's support activities for Great East Japan Earthquake victims (2013)

June

First Board of Councilors meeting held.

August

Agreement signed with Fukushima Medical University for collaboration and cooperation in the areas of education, research, and health.

2012-2017

2012

April

RERF reorganized as public interest incorporated foundation.

2013

April

Biosample Center (present-day Biosample Research Center) established for centralized management and future research utilization of biological (blood, urine, etc.) samples provided by A-bomb survivors and their children.

Biosample Center

Liquid nitrogen tanks for storing biological samples (lymphocytes)

2014

April

Sample storage begins at Biosample Center (present-day Biosample Research Center).

October

Epidemiological Study of Health Effects in Fukushima Emergency Workers (NEWS: NEW Study) commissioned by the Ministry of Health, Labour and Welfare in the framework of its occupational disease clinical research subsidy.

2018-2022

2018

May

First meeting of Stakeholder Committee on Usage of RERF's Stored Biosamples (4 meetings held through September 2019).

June

The 70th Anniversary Commemorative Event of ABCC-RERF (Nagasaki).

August

First External Advisory Committee on Biosample Usage held in Nagasaki (3 meetings held through October 2019).

Atmosphere at the venue (Nagasaki)

2019

February

Discussions held between U.S.-Japan experts regarding new organ dose estimation in US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki project.

June Ninth meeting of the Board of Councilors held (scene at National Academy of Sciences, in Washington, DC)

2023-2025

2023

June

External Advisory Committee on Biosample Usage held (2 meetings held through August 2023).

October

New dosimetry methodology developed in consideration of age, sex, and anatomical organ information.

2024

April

Public lecture in Hiroshima and Nagasaki (theme: parental radiation exposure and children's health; total of 3 lectures held in Hiroshima, Nagasaki).

Briefing session for participants (parental exposure and children's health; total of 3 sessions held in Hiroshima, Nagasaki).

December

Nobel Peace Prize awarded to Japan Confederation of A- and H-Bomb Sufferers Organizations.

RERF held International Symposium on Ethical, Legal, and Social Issues (ELSI) regarding Return of Results for Genome Studies of Atomic Bomb Survivors.

Public lecture in Hiroshima

Public lecture in Nagasaki

2015

October

Introduction of robot-type freezers (ultra-low-temperature automatic sample transfer refrigerator) for greater efficiency and safety in biosample storage.

Robotic freezer
(BioStore™ II by Brooks)

2016

April

Launch of outreach program at local schools for dissemination of radiation-related knowledge.

At elementary and junior high schools in Hiroshima City

2017

June

70th Anniversary Commemoration of ABCC-RERF held in Hiroshima.

Lecture by Mr. Sunao Tsuboi, Chairman of the Hiroshima Prefectural Confederation of A-bomb Sufferers Organizations

2020

COVID-19 pandemic.

November

Advice received from the External Advisory Committee on sample usage.

Advisory Acceptance Ceremony

2021

August

First online Open House following cancellation in 2020 due to the COVID-19 pandemic.

First External Advisory Committee on Genome Sequencing Analysis of A-bomb Survivors' Children (Hiroshima, Nagasaki)
(5 meetings held through April 2022).

2022

August

Ambassadors who attended the Hiroshima Peace Memorial Ceremony visited the Hiroshima Laboratory. Since then, it has become an annual tradition.
Over the course of three visits through 2024, a total of 107 individuals from 73 countries, regions, and organizations have visited the institute.

2025

**80th commemoration of atomic bombings,
50th anniversary of RERF's establishment.**

April

Signing of collaborative reseach agreement with Hiroshima University Hospital.

March RERF 52nd Scientific Advisory Committee Meeting held

I Research Activities

Overview of RERF's Major Research Programs

To obtain high-quality data on late effects from exposure to radiation from the atomic bombings, it is necessary to conduct an epidemiological study that follows fixed populations of both exposed and unexposed individuals to observe whether an excess of specific events occurs in the exposed population. ABCC–RERF has established study groups of A-bomb survivors, survivors exposed in utero, and children of A-bomb survivors (second-generation A-bomb survivors) and is following up these groups to understand whether radiation exposure is associated with long-term health effects.

A. Studies of A-bomb Survivors

Life Span Study (LSS)

Following the recommendations of the Francis Committee in 1955, the LSS cohort, a study population developed to investigate the mortality experience of A-bomb survivors, was established. A supplemental survey conducted at the time of the 1950 national census identified approximately 284,000 A-bomb survivors throughout Japan (excluding Okinawa and Amami Oshima). Of that number, approximately 200,000 A-bomb survivors who were living in Hiroshima or Nagasaki at the time of the survey as well as people who were not in either city at the time of the atomic bombings were included in the baseline study population and were asked in interviews about their situation at the time of the bombings. The initial LSS cohort consisted of the following groups of Japanese people included in the baseline population and whose legal residence was in Hiroshima or Nagasaki City: Group 1, all those who experienced the atomic bombing within 2,000 meters of the hypocenter*; Group 2, all those who experienced the bombing at 2,000–2,499 m from the hypocenter; Group 3, those who experienced the bombing at 2,500–9,999 m from the hypocenter; and Group 4, those who were at least 10,000 m from the hypocenter at the time of the bombing (those who were not in the cities at the time of the bombing). Groups 3 and 4 were selected by matching to Group 1 in terms of sex and age. With that, the LSS cohort consisted of a total of 99,382 people. Additional recruitments of subjects were made twice (expanded LSS cohort), bringing the total study population to 120,321 individuals. The population consists of 93,741 people who experienced the atomic bombing within 10,000 meters of the hypocenter and 26,580 people who were not in the cities at the time of the bombing. The study continues to investigate the association between radiation exposure and cancer incidence as well as mortality.

Adult Health Study (AHS)

The AHS is a clinical research program following a group of LSS participants. When established in 1958, the AHS study population comprised the following four groups (totaling 19,961 individuals): Group 1, 4,998 survivors who were exposed to radiation within 2,000 meters of the hypocenter and exhibited acute symptoms; Group 2, 4,975 survivors who were exposed within 2,000 meters of the hypocenter but did not exhibit acute symptoms; Group 3, 4,988 survivors who were exposed at 3,000–3,499 meters from the hypocenter in Hiroshima and 3,000–3,999 meters in Nagasaki; and Group 4, 5,000 persons who were not in the cities at the time of the bombing. All eligible survivors were included in Group 1. For Groups 2–4, a similar number of members were selected for each group by matching to Group 1 by city, sex, and age. The AHS cohort has been expanded several times since its establishment. The newly added subjects include 1,021 people from the

clinical study group of in utero survivors (see below). To date, the total number of people who have participated in the AHS study is 25,379. Health studies of the 5,000 people who were not in the cities at the time of the atomic bombing were concluded in 1977.

AHS participants are asked to visit the clinic once every two years to undergo health examinations. The examinations include measurements of blood pressure, height, and weight, as well as blood testing, chest X-rays, and abdominal ultrasound. When necessary, additional specialized tests—such as bone density measurements or gynecological exams—are also carried out. Using the collected data, RERF conducts long-term follow-up studies on the prevalence and incidence of various diseases, as well as changes in test results over time. Information on each participant's medical history (including illness, exam, and treatment information) and lifestyle habits (such as alcohol consumption and smoking) is also collected. Such factors are taken into account when assessing health effects of radiation exposure. The health examination results are provided to each participant for use in their own health management.

B. Studies of In Utero Survivors

Two study populations of in utero survivors—the mortality follow-up study cohort and the clinical study cohort—were established using different sampling methods.

The mortality follow-up study cohort of in utero survivors consists of the following five groups of children, a total of 2,802 people, who were born between the day of the atomic bombing and the end of May 1946: Group 1, all in utero survivors whose mothers were exposed to A-bomb radiation within 1,500 meters of the hypocenter; matching with Group 1 in terms of city, sex, and birth month, Groups 2, 3, and 4, in utero survivors whose mothers were exposed at 1,500–1,999 m, 2,000–2,999 m, and 3,000–9,999 m from the hypocenter, respectively; and Group 5, those who were not exposed in utero.

The clinical study cohort of in utero survivors consists of the following three groups of people, a total of 1,606 individuals who were living in Hiroshima City or Nagasaki City in 1950: Group 1, all in utero survivors whose mothers were exposed to A-bomb radiation within 2,000 m of the hypocenter; Group 2, in utero survivors whose mothers were exposed at 3,000–4,999 m from the hypocenter; and Group 3, those whose mothers were not in the cities at the time of the bombing. Groups 2 and 3 were selected by matching to Group 1 by city, sex, and birth month. Follow-up of these study populations was suspended around 1965 but was later resumed, in 1978, after the addition of 1,021 participants, excluding those who had died or whose mothers were not in the cities at the time of the atomic bombing, to the AHS program.

There are people who belong to both of the aforementioned cohorts, and a mortality follow-up study is now being conducted of the combined 3,638 in utero survivors. This study investigates the association between radiation exposure and cancer incidence as well as mortality.

C. Study of the Children (F_1 Offspring) of A-Bomb Survivors

Mortality study

ABCC's early studies focused on genetic effects in the children of A-bomb survivors, and included a study of birth defects and early mortality in approximately 77,000 newborns between 1948 and 1954, followed in 1962 by a study of sex ratios in approximately 71,000 newborns.

Based on the need for continued follow-up of children of A-bomb survivors, a mortality study

cohort was established. The following three groups consisted of single birth babies born between May 1946 and December 1958: Group 1, all children one or both of whose parents were exposed to A-bomb radiation within 2,000 m of the hypocenter; Group 2, children one or both of whose parents were exposed at 2,500–9,999 m from the hypocenter; and Group 3, children whose parents were not in the cities at the time of the bombing. For Groups 2 and 3, almost the same numbers of children matched to Group 1 by sex and age were selected, with a total of 53,519 children of A-bomb survivors included in the groups. Subsequently, 23,295 children from the expanded LSS cohort who were born between January 1959 and December 1984 were added to the mortality study cohort, making a total study population of 76,814 children of A-bomb survivors, who are currently being followed up. This study investigates the association between parental radiation dose and cancer incidence as well as mortality in their children.

Clinical studies

To investigate the relationship between radiation exposure and multifactorial diseases developing in adulthood such as hypertension and diabetes in the children of A-bomb survivors, the Health Effects Study of the Children of A-bomb Survivors was initiated and followed by the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors.

The Health Effects Study of the Children of A-bomb Survivors consists of a mail survey and a clinical health study. Among 76,814 subjects of the mortality study cohort of the children of A-bomb survivors, subjects were selected and assigned to the following four groups based on the radiation exposure dose calculated using the Dosimetry System 1986 (DS86): Group 1, children whose parents' radiation dose was estimated and one or both of whose parents received a radiation dose of ≥5 mGy; Group 2, children at least one of whose parents received a radiation dose of ≥1 Gy; Group 3, children both of whose parents were exposed to radiation but the radiation doses were unknown; and Group 4, children both of whose parents received radiation doses of <5 mGy or were unexposed and selected by matching to the subjects of Groups 1–3 by city, sex, and year of birth. From among these groups, a total of 24,673 children of A-bomb survivors were selected also in consideration of their legal residence and current address, with mail surveys conducted between 2000 and 2006. Of 14,145 people who consented to undergo health examinations based on mail survey questionnaire, 11,951 participated in the clinical health study (prevalence study) between 2002 and the end of September 2006. In this study, medical history and lifestyle habits were assessed through interviews, and health examinations including blood pressure measurement, electrocardiograms, blood testing, and abdominal ultrasound were conducted.

In this prevalence study, the children of A-bomb survivors examined were relatively young, with a mean age of 49 years, and had just entered the peak age for disease onset. As prevalence studies are more prone to bias, RERF's Scientific and Ethics Committee for the Health Effects Study of the Children of A-bomb Survivors, the Scientific Advisory Committee, and the Senior Review Panel (a special evaluation committee composed of external experts) recommended that the survey be continued.

Based on this recommendation, the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors, based on cycles of health examinations conducted every four years, was initiated in 2010. Among the people who consented to undergo health examinations based on the questionnaire of the Health Effects Study of the Children of A-bomb Survivors, 13,100 people who were alive at the start of the longitudinal study with known addresses were selected as study participants. As in the AHS, this study conducts health examinations including measurements of blood pressure, height, and weight, blood testing, chest X-rays, and abdominal ultrasound to investigate the prevalence and incidence of diseases. The health examination results are provided to each participant for use in their own health management.

D. Radiation Dosimetry

The Radiation Effects Research Foundation (RERF) scientifically estimates the radiation doses that atomic bomb survivors received in Hiroshima and Nagasaki to evaluate the health effects of atomic bomb radiation. The estimation of radiation dose for atomic bomb survivors is based on three key components: (1) the output of radiation from the atomic bomb, (2) the attenuation of radiation as it traveled to each survivor's location (exposure distance), and (3) shielding effects determined by the survivor's specific circumstances at the time of exposure. Measurements related to the bomb's output, atmospheric attenuation, and shielding by buildings were obtained from nuclear tests conducted in the Nevada desert, known as the Ichiban Project.

Information about each survivor's location and surrounding environment at the time of exposure was gathered through interviews conducted between 1949 and 1965 with the survivors and their families. Based on deliberations among Japanese and American experts, the dose estimation system has been continuously improved over time with advances in scientific technology.

Tentative 1957 Dosimetry System (T57D):

A simple dose curve based on distance from the hypocenter was applied for each city, along with basic shielding assumptions.

Tentative 1965 Dosimetry System (T65D):

Proposed in the 1960s and revised in the 1970s, this system was based on measured data from the Ichiban project. The doses were referred to as "provisional" because of recognized limitations in both the data and calculation methods.

Dosimetry System 1986 (DS86):

With the development of computers, this system was able take into account more precise shielding conditions. By incorporating information such as body position at the time of exposure, the system enabled detailed estimates of radiation doses to individual organs for each of the survivors, providing a highly sophisticated framework.

Dosimetry System 2002 (DS02):

Introduced in 2002, this improved version of DS86 looked into consistency between DS86 estimates and the actual measurements of residual radioactivity that had been collected in Hiroshima.

DS02 Revision 1 (DS02R1):

Implemented in 2017, this revision involved recalculations based on improved data such as more accurate survivor location coordinates. It is currently used in epidemiological and clinical research.

Alongside these physics-based dose estimations, biological methods for estimating radiation exposure based on traces left in the human body have also been developed. Since 1966, chromosome analysis in lymphocytes has been conducted to evaluate and complement physical dose estimates.

Chromosomes consist of long, interconnected DNA molecules. When cells are exposed to radiation or carcinogenic substances, DNA strands may break, and during the repair process, they can be rejoined in an incorrect structure. These structural abnormalities in chromosomes, known as chromosomal aberrations, increase in proportion to the radiation dose to which the cell is exposed.

Additionally, radiation dose can be estimated by measuring CO_2– radicals retained in tooth enamel using the Electron Spin Resonance (ESR) method. Comparisons between biologically estimated doses and physically simulated dose calculations have been conducted to further refine radiation exposure assessments.

E. Molecular Biology Research

Molecular biology research contributes to RERF's mission by investigating the mechanisms of radiation effects observed in clinical and epidemiological studies. The main objectives are to elucidate the molecular mechanisms of diseases associated with radiation exposure and to investigate the transgenerational effects of radiation exposure through collaborative research within RERF and with external research institutes (Figure 1).

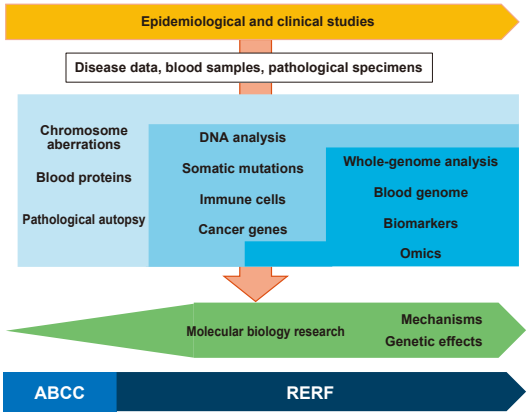


Figure 1. Overview of Molecular Biology Research

Molecular genetics and cellular genomics

Chromosome studies in atomic bomb (A-bomb) survivors began in 1966 and have demonstrated that the proportion of blood T lymphocytes with stable chromosome aberrations increases significantly with increasing radiation dose. Current research involves using chromosome aberrations as indicators to estimate biological radiation doses and to understand the mechanisms of radiation effects on the hematopoietic system. Analyses of chromosome aberrations and mutations in specific blood proteins and DNA fragments in children of A-bomb survivors showed no increase in aberrations or mutations due to parental radiation exposure. At present, preparations are underway for new research focusing on DNA analysis across the entire genome (whole-genome analysis). This research is expected to provide more detailed insights.

Hematopoietic and immune systems

The hematopoietic and immune systems are highly susceptible to radiation-induced cell damage. Chromosome aberrations and DNA mutations in the blood cells of A-bomb survivors have been shown to increase with radiation dose even decades after exposure. Therefore, hematopoietic function and immune cells are being analyzed in participants of the Adult Health Study. Blood cells, especially immune cells, circulate throughout the body and play a role in controlling inflammation and defending against pathogens and cancer cells. These cells are thought to be involved in the mechanisms underlying the development of various diseases whose risk increases with radiation exposure. Research on the effects of radiation on the hematopoietic and immune systems could help identify biomarkers for such diseases.

Radiation-related cancers

The Life Span Study (LSS) has shown that the risk of radiation-induced cancer varies by organ, sex, and age at exposure. These differences may be associated with variations in DNA changes in radiation-exposed cells and in their growth ability. DNA changes in specific cancer-related genes have thus been investigated using pathological specimens collected from the LSS. RERF also implements omics-based research, including the analysis of tumor cell proteins, to elucidate the underlying mechanisms of radiation carcinogenesis and to identify new biomarkers.

2 Major Program Achievements Over 50 Years

A. Studies of A-bomb Survivors

Life Span Study (LSS)

Malignant neoplasms

1 Leukemia and related diseases

An increase in cases of leukemia was the earliest late effect of radiation exposure observed in A-bomb survivors. Because the follow-up of the LSS cohort began in 1950, five years after the bombing, no data are available for the time before that year. However, reports from medical facilities indicate that the increased risk of leukemia due to radiation exposure began to appear approximately two years after the bombings. It is estimated that the risk increase in the LSS cohort peaked seven to eight years after exposure and then declined continuously, but the increased risk does not appear to have disappeared completely, even more than 50 years after the bombings. Of the four major leukemia subtypes, acute myelogenous leukemia [AML], acute lymphatic leukemia [ALL], chronic myelogenous leukemia [CML], and chronic lymphatic leukemia [CLL]), risk increases among A-bomb survivors were confirmed for all subtypes except for CLL.[1] An analysis of the incidence of all leukemia types excluding CLL and adult T-cell leukemia (ATL) during the period 1950–2001[2] indicated that the higher the radiation dose was, the steeper the increase in risk and showed a concave dose-response curve. In the analysis, the ERR at age 70 after exposure to 1 Gy at age 30 is estimated to be 1.74 (Figure 2). Because the incidence of AML is the highest among the four major subtypes, the results for all leukemias tend to mirror the results for AML.

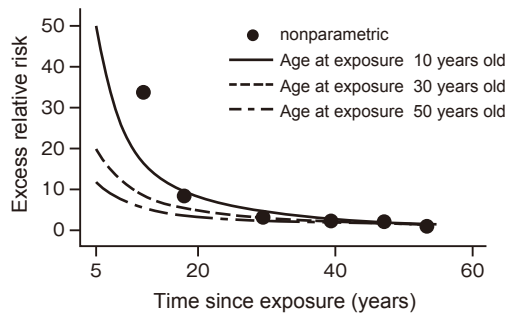


Figure 2. Change in sex-averaged ERR of leukemia (excluding CLL and ATL) as related to age at exposure and time since exposure for people who were exposed to 1 Gy[2]

Table 1 shows the observed numbers of all leukemia cases, excluding CLL and ATL, as well as the estimated number of excess cases in the LSS cohort by bone marrow dose during the period 1950-2001. It is estimated that 94 of the 192 leukemia cases exposed to ≥0.005 Gy are related to radiation exposure, with the attributable fraction being 49%. Among heavily exposed survivors of ≥1 Gy, 57 of 64 cases are estimated to be related to radiation exposure, with that attributable fraction being 89%.

The mortality study[3] showed significantly elevated risk of malignant lymphoma among males (ERR/Gy = 0.70, 95% CI: 0.08, 1.7) but no elevated risk among females (ERR/Gy = -0.18, 95% CI: -0.21, 0.24). Similar trends have been observed with non-Hodgkin lymphoma in incidence studies[2] and studies[4] including a review of pathology data and samples. Approximately 90% of cases of malignant lymphoma in Japan are comprised of non-Hodgkin lymphoma. There is no clear explanation for the differences between males and females.

In the mortality study,[3] a significant risk increase for multiple myeloma was observed among females (ERR/Gy = 0.86, 95% CI: 0.02, 2.5). The ERR/Gy for males was 0.11 (95% CI: -0.28, 1.6), and the risk increase was not significant. At the same time, an incidence study[2] and a study[4] including a review of pathology data and samples showed no difference in risk between males and females or no significant risk increase

Table 1. Observed numbers of all leukemia cases, excluding CLL and ATL, and the estimated number of excess cases in the LSS cohort (1950-2001)[2]

Dose (Gy)	Person years	Mean dose (Gy)	Observed cases	Fitted cases*	
				Background	Excess
<0. 005	2, 039, 093	0. 0006	120	116. 9	0. 1
0. 005–0. 1	957, 889	0. 03	63	60. 7	3. 6
0. 1–0. 2	201, 935	0. 14	16	13. 7	4. 1
0. 2–0. 5	206, 749	0. 32	25	13. 6	11. 1
0. 5– 1	117, 855	0. 71	24	7. 5	18. 2
1 – 2	64, 122	1. 37	35	4. 0	28. 4
2 +	25, 761	2. 68	29	1. 5	28. 6
Total	3, 613, 404	0. 10	312	217. 9	94. 1

* Estimated number of cases calculated by fitting the model selected in reference[2]

(ERR/Gy = 0.38, 95% CI: -0.23, 1.36).

In a study[4] that included a review of pathology data and samples, the classification of lymphoma, which has changed over time, was reclassified into WHO subtypes through reviews conducted by pathologists, with an analysis conducted for each subtype. There was a strong relationship between the incidence of precursor lymphoblastic lymphoma and radiation dose (males, ERR at 1 Gy = 55, 95% CI: 9.5, 620; females, ERR at 1 Gy = 6.4, 95% CI: 0.6, 30), suggesting that the observed relationship between radiation exposure and incidence of lymphoma primarily reflects radiation effects on precursor lymphoblastic lymphoma.

2 Solid cancers

For solid cancers, RERF has also reported mortality,[3] but because there are some cancers that have a relatively small impact on prognosis for survival, such as thyroid cancer and skin cancer, we mainly present the results from solid cancer incidence surveys[5] and follow-ups performed between 1958–2009.

Among the LSS cohort, 105,444 people who were not in the cities at the time of the bombings or who were in the cities at the time of the bombings with estimated DS02R1 dose, and who were alive in 1958 when cancer registries were initiated in Hiroshima and Nagasaki, and had not been diagnosed with cancer before that time, were examined and first primary solid cancers were diagnosed in 22,538 people during that period. The risk of cancer development varies depending on age and sex but is also affected by other factors. Therefore, based on the mail surveys and AHS interviews performed thus far, we conducted analysis by adjusting for such factors as lifestyle habits such as smoking and drinking, degree of obesity, and reproductive factors to the extent possible.

As with previous studies, the results demonstrated that radiation is associated with risk of all solid cancers, even more than 60 years after the atomic bombings. The risk of cancer incidence has previously been shown to increase linearly with radiation dose, but observations during 1958–2009 revealed differences in dose-response between males and females. In females, the dose-response risk increased linearly with dose, as previously reported, with the ERR/Gy estimated to be 0.64 (95% CI: 0.52, 0.77). In males, the dose-response curve was upward sloping, and the ERR at 1 Gy and 0.1 Gy was estimated to be 0.20 (95% CI: 0.12, 0.28) and 0.010 (95% CI: -0.0003, 0.021), respectively. Consistent with previous studies, the risk of cancer incidence of A-bomb survivors varied depending on sex, age at exposure, and attained age (time since exposure). Regarding the risk of cancer incidence at age 70 after exposure to 1 Gy, for example, participants who had been younger at the time of exposure had a higher ERR and excess absolute risk (EAR), suggesting that younger people are more sensitive to radiation.

Figure 3 shows ERR (excess relative risk) per 1 Gy and its confidence intervals for all

solid cancers and by cancer site. Since ERR varies by sex, age at exposure, and attained age, the risks presented represent averages for males and females, assuming exposure at age 30 and attained age of 70. For breast, corpus uteri, cervix, and ovary cancers, the risks are shown for females only, while prostate cancer risk is shown for males only. Additionally, thyroid cancer risk is presented for exposure at age 10 and attained age of 60.

The ERR per 1 Gy for all solid cancers, averaged for both sexes, is estimated to be 0.47 (95% CI: 0.39, 0.55), indicating that rate of cancer incidence is estimated to increase 47% at 1 Gy of radiation exposure compared to unexposed individuals. As shown in the figure, exposure to 1 Gy of A-bomb radiation was significantly associated with increased risk of cancer incidence in the following organs: central nervous system,[6] urinary tract/bladder,[7] thyroid,[8] female breast,[9] lung,[10] corpus uteri,[11] salivary glands,[12] colon,[13] liver,[14] prostate,[15] pancreas,[14] stomach,[12] and esophagus.[12]

On the other hand, no statistically significant increase in cancer risk was observed for ovary,[16] pharynx and other oral cavity sites,[12] larynx,[12] rectum,[13] cervix,[11] or bile duct.[14] These results suggest possible differences in radiation sensitivity by organ site. However, because the confidence intervals for many sites overlap, statistical evidence for differences in ERR by cancer site remains insufficient, so caution is warranted when interpreting the data.

The estimated number of excess cancer cases per 1 Gy of exposure is 54.7 per 10,000 person-years for females and 42.9 per 10,000

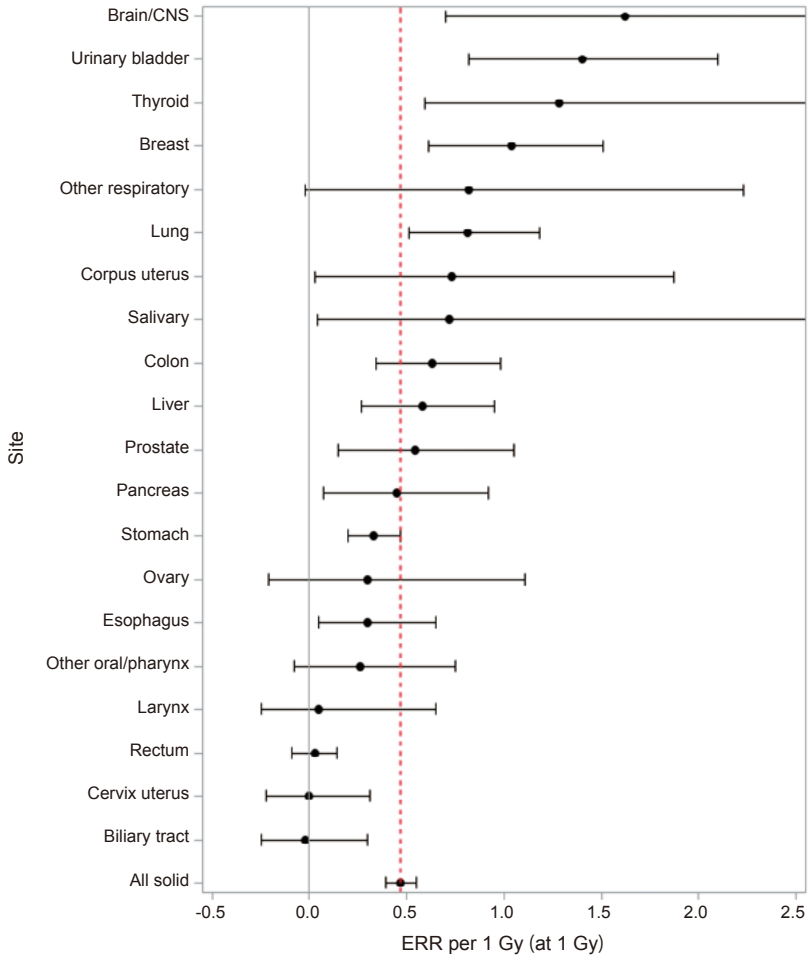


Figure 3. Sex-averaged excess relative risk per 1 Gy for site-specific cancer incidence in the LSS cohort (for thyroid cancer, assuming exposure at age 10 and attained age of 60; for other cancers, assuming exposure at age 30 and attained age of 70).

person-years for males.[5]

When comparing ERR and estimated excess incidence for leukemia and solid cancers, ERR per 1 Gy is higher for leukemia, but the estimated number of excess cases is greater for solid cancers. This is because, although leukemia has a strong association with radiation, it is a relatively rare cancer compared to solid cancers. Therefore, the impact on the overall population is less for leukemia than for all solid cancers combined. In contrast, because the baseline incidence of all solid cancers combined is higher than that of leukemia in the absence of radiation exposure, the estimated number of excess cases is larger, indicating a greater impact on the population.

Other than malignant neoplasm

Reports from studies of mortality in the LSS cohort, which began as the report "JNIH-ABCC Life Span Study," continue to be prepared even after the ABCC was reorganized into RERF, with Nos. 8 to 14[3] published to date. During this time, the radiation dosimetry system was revised from T65D to DS86, and then to DS02. Statistical methods have also changed, from analyses based on cross-tabulation tables to Poisson regression analysis. As the observation period has become longer, more detailed examinations have been performed, including on the shape of the dose-response relationship, duration, and effect-modifying factors.

Regarding death from diseases other than malignant neoplasms, a follow-up until 1978[17] showed no significant increased risk, excluding hematologic diseases (since these might have included misclassified hematopoietic malignancies). However, LSS Report No. 11,[18] based on follow-up information until 1985, reported a significant increase in risk of death from all diseases except malignant neoplasms and blood diseases, as well as an increased risk of death from circulatory and digestive diseases in the high-dose exposure group. In report No. 14,[3] mortality risks from cardiovascular diseases (ERR/Gy = 0.11, 95% CI: 0.05, 0.17) and respiratory diseases (ERR/Gy = 0.21, 95% CI: 0.10, 0.33) were significantly increased. In the first half (1950–1965) of the observation period, the risk for each of these diseases was increased only at high doses, and in the second half (1966–2003), an approximately linear dose-response relationship was reported.

Studies using preserved samples

Special cancer studies

The Adult Health Study (AHS) collects clinical and epidemiological information on health status through biennial health examinations and has preserved sera (since 1969), plasma and blood cells (since 1990), and urine (since 1999) provided by AHS participants for future cancer and non-cancer research. The Life Span Study (LSS) has shown that radiation exposure is associated with increased risks of cancers of the breast, stomach, liver, and others; however, these findings did not fully account for other risk factors, such as hormones and pathogens. Nested case-control studies using blood samples collected before cancer diagnosis in the AHS are useful for investigating how these risk factors could modify the effects of radiation on the risk of cancers such as breast cancer, gastric cancer, and hepatocellular carcinoma (HCC), which accounts for the majority of liver cancer.

1 Breast cancer

High levels of estradiol and progesterone are known risk factors for breast cancer. A case-control study using preserved sera from AHS participants showed that radiation exposure, high levels of estradiol (bioavailable estradiol, bE2), testosterone, and progesterone, and reproductive risk factors were positively associated with postmenopausal breast cancer risk, with a suggestion that some radiation effects could be mediated by bE2.[19] Taken together, it is suggested that radiation might impact breast cancer risk not only through DNA damage but also by altering the hormonal environment.

2 Stomach cancer

Helicobacter pylori (Hp) infection and chronic atrophic gastritis (CAG) are known risk factors for noncardia gastric cancer. Cytotoxin-associated gene A (CagA), a virulence factor secreted by Hp, plays an important role in its pathogenesis.

A case-control study using preserved sera from AHS participants demonstrated that anti-Hp IgG seropositivity with low anti-CagA IgG titers was the strongest risk factor for noncardia gastric cancer, and the risk was particularly elevated for the intestinal type.[20] Radiation exposure was also shown to be associated with an increased risk of diffuse-type noncardia gastric cancer without CAG. This association remained significant after adjustment for Hp infection and smoking habits.[21] These results indicate that CagA, CAG, and radiation exposure affect the risk for noncardia gastric cancer. Further elucidation of the interactions between these factors is required.

3 Hepatocellular carcinoma (HCC)

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major risk factors for HCC. In a case-control study using preserved sera from AHS participants, controls were selected by matching to HCC cases on gender, age, location of exposure, and serum preservation method, and by countermatching on radiation dose. Controls were selected using cohort stratification according to radiation exposure dose. After adjustment for alcohol consumption, BMI, and smoking, the relative risk of HCC was 1.67 for 1 Gy exposure, 63 for HBV infection, and 83 for HCV infection. The adjusted relative risk for non-B non-C HCC was 2.74.[22] The results also showed that radiation exposure and HBV and HCV infections are independently associated with an increased risk of HCC and that HCV infection and increased BMI act synergistically.[23] HCC risk was also associated with high serum IL-6 levels, and this association was particularly strong in obese individuals.[24] HCV infection may cause hepatic steatosis and insulin resistance and, in association with chronic inflammation from radiation exposure and obesity, could be considered to potentially promote hepatocarcinogenesis. However, further research is needed to elucidate the underlying mechanisms.

Non-cancer diseases and disorders

Since 1958, the Adult Health Study (AHS) has conducted biennial health examinations on participants after obtaining their informed consent. Since the start of the study, the health examination has included a medical history review, an interview on lifestyle habits, physical measurements, blood pressure measurement, electrocardiogram, blood tests (hematology), urinalysis, and a chest X-ray. Since the 1980s, it has also included blood tests (biochemistry), ultrasound, and fecal occult blood testing. Although the attendance rate has declined due to the aging of the survivor population and the impact of the COVID-19 pandemic, RERF continues efforts to maintain the attendance rate for health examinations. Diseases diagnosed during regular health examinations are coded according to the International Classification of Diseases, facilitating the understanding of the occurrence of many non-cancer diseases.

Using diagnoses based on regular health examinations of the original cohort of approximately 10,000 individuals, the relationship between the incidence of non-cancer diseases and radiation dose has been reported for the periods from 1958 to 1986[25] and 1958 to 1998.[26] Similar to the findings in the 1958–1986 report,[25] the 1958–1998 report[26] showed an increase in thyroid disease, chronic liver disease including cirrhosis, and uterine myoma due to radiation exposure (with a significant dose-response relationship). In addition, a significant positive linear dose-response relationship was reported for cataracts. While no effect of radiation exposure was observed under a linear dose-response model on cardiovascular diseases, including hypertension, ischemic heart disease, myocardial infarction, and stroke, a quadratic dose-response relationship was suggested between radiation exposure and hypertension as well as myocardial infarction in A-bomb survivors exposed before the age of 40 years old.[26]

Although the Life Span Study (LSS) mortality study showed an association between radiation and a shortened life span among A-bomb survivors, the AHS prevalence and incidence studies did not report any effects of radiation

exposure on age-related diseases.[25,26] Further analyses over a longer period will continue.

There are several limitations to interpreting the AHS results for non-cancer diseases. Since the study is conducted with participants who take part in the health examinations, cases cannot be identified in individuals who are unable to participate due to diseases with a high rate of mortality or significant sequelae. It should also be noted that many factors contribute to non-cancer diseases, and complete information on such factors is not yet available. Additionally, the rapid westernization of the Japanese lifestyle and changes in medical technology after the war may have modified the occurrence of disease in a complex manner.

The AHS has also collected data on diagnosed diseases as well as other information such as changes in test values leading up to the onset of disease. Increases in total cholesterol levels in A-bomb survivors,[27] and in blood pressure levels[28] in A-bomb survivors born after 1930 have been reported. In addition, special clinical studies have been conducted, including prevalence studies based on detailed investigations over a limited period and incidence studies for diagnoses using the uniform diagnostic criteria. The results of these studies will be described in the sections that follow.

Special clinical studies

1 Cardiovascular diseases

Cardiovascular diseases include stroke, myocardial infarction, and a variety of other specific cardiovascular conditions. Observations worldwide have shown an increase in arterial stenosis and heart disease following high-dose radiation from radiotherapy. This may be due to radiation-induced tissue damage (cell death) and the accompanying biological response. Meanwhile, exposure to lower doses of radiation has been associated with an increased risk of death from cardiovascular disease among atomic bomb survivors in the LSS, although the underlying mechanisms remain unclear.

a. Mortality from cardiovascular disease

Data from the Life Span Study (LSS) cohort (86,611 subjects from 1950 to 2003) based on the latest DS02 dose estimates showed an 11% increase in mortality from cardiovascular disease per 1 Gy (ERR/Gy = 0.11, 95% CI: 0.05, 0.17).[3] A statistically significant association was also observed for stroke (ERR/Gy = 0.09, 95% CI: 0.01, 0.17) and heart disease (ERR/Gy = 0.14, 95% CI: 0.06, 0.23).[29] However, these associations were not significant when the dose range was limited to 0.5 Gy or less.

Although the reliability of death certificates is often a concern in the LSS, the association between radiation exposure and heart disease as a whole has been consistently observed even after 1995, when diagnostic accuracy improved.[30] On the other hand, it is too early to draw any conclusions about the association between radiation exposure and stroke or other specific cardiovascular diseases because of the high rate of misclassification in death certificates of cardiovascular diseases during earlier periods.

b. Incidence of cardiovascular disease

The health examinations conducted as part of the AHS include electrocardiogram testing which, when combined with medical history, are expected to provide more accurate understanding of the occurrence and classification of cardiovascular disease. For this reason, the AHS has led the field of radiation-related cardiovascular epidemiology in Japan since its inception.[31] In particular, the NI-HON-SAN Study[32] is acclaimed worldwide for demonstrating the importance of lifestyle habits in the occurrence of ischemic heart disease and stroke.

To date, no reproducible association between specific cardiovascular diseases and radiation exposure has been observed in the AHS. However, an association has been suggested under certain limited conditions. For example, an association has been observed with incidence of myocardial infarction in A-bomb survivors who were exposed before the age of 40 years old,[26] as well as a gender difference (linear response for men; response with threshold for women) in the association between radiation exposure

and incidence of hemorrhagic stroke.[33] Further research progress is anticipated in the future, including mechanistic studies using biomarkers.

2 Liver diseases

a. Hepatitis virus infection

Radiation exposure dose has been associated with an increased prevalence of hepatitis B virus (HBV) antigen among atomic bomb survivors, while no evidence has so far been obtained for its association with hepatitis C virus (HCV) antibody.

Of four large-scale studies conducted as part of the AHS (1969–1970,[34] 1975–1977,[35] 1979–1981,[36] and 1993–1995,[37] respectively), the first[34] showed no significant association between radiation exposure dose and the prevalence of hepatitis-related antigen (currently known as HBs antigen). The subsequent three studies found that the prevalence of HBs antigen increased with increasing radiation exposure dose and tended to increase with decreasing age at exposure. In particular, among A-bomb survivors who had received blood transfusions between 1945 and 1972, the prevalence of HBs antigen increased with increasing radiation exposure dose.[37] These findings suggest that radiation exposure might have impaired immune function, reducing the body's ability to eliminate HBV.

The study of HCV infection conducted from 1993 to 1995[38] as part of the AHS showed that the prevalence of HCV antibody was clearly lower in individuals exposed to a radiation dose greater than 0 Gy compared to those exposed to 0 Gy. A similar trend was observed in the association between the radiation exposure dose and high HCV antibody titers, an indicator of current infection. Of note, since HCV was discovered in 1989, many HCV-positive A-bomb survivors might have already died of liver cirrhosis or hepatocellular carcinoma by the time of this study; therefore, the results should be interpreted with caution.

b. Liver cirrhosis

As described above, comprehensive studies in the AHS during the periods 1958–1986 and 1958–1998 showed that the incidence of chronic liver disease (including cirrhosis) increased by approximately 1.15 times per 1 Gy increase in radiation exposure dose, indicating a clear association. On the other hand, studies of causes of death and autopsy diagnoses conducted repeatedly as part of the LSS produced inconsistent results about the association between radiation exposure dose and deaths from liver cirrhosis. Even in a pathological study that accounted for the effects of HBV and HCV infections and alcohol consumption, no association was found between liver cirrhosis and radiation exposure dose.[39] For a more accurate assessment of radiation effects on liver disease, the main etiologies of liver disease such as HBV and HCV infection and fatty liver disease need to be taken into account.

3 Thyroid disease

Thyroid disease has been a focus of RERF research since the start of the AHS in 1958. A study conducted from 1974 to 1976, at around the time RERF was established, showed a higher incidence of thyroid cancer and nodules in the high-dose group; however, no correlation was found with thyroid-stimulating hormone levels, an indicator of hypothyroidism.[40]

In 1981, a thyroid program research protocol was developed at RERF that included epidemiological and pathological studies and basic research on thyroid cancer and clinical studies of benign and malignant thyroid diseases as part of the AHS. The thyroid study conducted between 1984 and 1987 in Nagasaki involved measurements of thyroid function and autoantibodies. Ultrasound examinations were also conducted for the first time using an automated scanner that captured transverse thyroid images at 5 mm intervals. An association was observed between the risk of solid nodules and adenomas and radiation exposure dose to the thyroid gland, whereas no association was found with hypothyroidism or hyperthyroidism. When analysis was limited to autoantibody-positive hypothyroidism, a dose-response relationship was observed, with the highest risk at 0.7 Gy.[41] The 1987–1989 study conducted in both Hiroshima and Nagasaki found

no association between thyroid autoantibodies and radiation exposure dose.[42]

The 2000–2003 study in Hiroshima and Nagasaki, the first comprehensive thyroid survey, involved measurements of thyroid function and autoantibodies, ultrasound examinations and, when necessary, fine-needle aspiration cytology.[43] The risks of solid nodules, cysts, cancer, and benign nodules larger than 1 cm increased with increasing radiation exposure dose to the thyroid gland and in individuals who were younger at exposure. Similar results were obtained in individuals exposed before the age of 10 years in the 2007–2011 study, when the AHS population was expanded.[44] On the other hand, both studies found no association between radiation dose and thyroid autoantibodies, autoantibody-positive or -negative hypothyroidism, or Graves' disease (hyperthyroidism).[43, 45]

Taken together, multiple cross-sectional studies have shown that radiation dose is consistently associated with thyroid cancer and benign nodules but not with thyroid dysfunction or autoantibodies. An ongoing longitudinal study initiated in 2018 has been conducting regular thyroid examinations among participants who were exposed before the age of 10 years old.

4 Cataracts

Among ocular tissues, the lens is the most susceptible to the effects of radiation exposure. An increased risk of cataract, a condition marked by opacity of the lens, has been reported in atomic bomb survivors from the early stages after exposure.[46] Ophthalmological studies conducted repeatedly since the days of the Atomic Bomb Casualty Commission (ABCC), the predecessor to RERF, have shown that radiation exposure is associated with an increase in posterior subcapsular opacification, a type of cataract in which the back of the lens becomes opacified. Since the establishment of RERF, ophthalmological studies have been conducted on the Adult Health Study (AHS) participants in the 1970s,[47] 2000s,[48] and 2010s. In the latest study, images of the lens were captured using standardized instruments based on the type of cataract and are digitally stored.

All these studies showed a significant association between radiation exposure and posterior subcapsular opacification; however, the results for other types of cataract have been inconsistent.

Given that studies conducted more than 70 years after the atomic bombings continue to suggest an association between radiation exposure and cataract, long-term follow-ups in other radiation-exposed populations are considered necesary.

5 Benign tumors

The AHS has investigated benign tumors of the uterus and the parathyroid and thyroid glands, all of which have been shown to be associated with radiation exposure.

Uterine myoma is a benign tumor of the uterine smooth muscle. The AHS has continuously investigated the incidence of non-cancer diseases based on diagnoses from regular health examinations. Studies conducted during the periods 1958–1986[25] and 1958–1998[26] showed an increased risk of uterine myoma with increasing radiation dose. In addition, a screening study using transabdominal ultrasound conducted in Hiroshima from 1991 to 1993 demonstrated an association between the risk of uterine nodules and maternal uterine radiation dose.[49]

Once a benign tumor (adenoma) develops in the parathyroid gland, it secretes excessive parathyroid hormone, leading to a condition called primary hyperparathyroidism. This disorder is associated with high blood calcium levels, reduced bone density, and impaired renal function. A study conducted in Hiroshima from 1986 to 1988 involved the screening of blood calcium levels. For individuals with elevated blood calcium levels, a parathyroid hormone test and other relevant tests were conducted. The results showed an association between the risk of primary hyperparathyroidism and radiation exposure, with a suggestion of higher radiation-related risk in individuals who were younger at the time of exposure.[50] Currently, blood calcium levels are measured for all participants

during regular health examinations in the AHS conducted in Hiroshima and Nagasaki.

For information on benign thyroid tumors (benign nodules), please refer to the section on thyroid disease.

6 Growth, development, and bone disease

In early studies conducted by ABCC, physical measurements (e.g., height, weight, chest circumference) were made with the aim of assessing radiation effects on growth and development in survivors who had been exposed as children. From 1947 to the 1950s, comparison studies were conducted using children in Kure and Sasebo as controls, or between groups stratified by distance from the hypocenter. The results showed that exposure to atomic bomb radiation during childhood caused growth impairments.

In the 1990s, the accumulated data were analyzed longitudinally. Changes in height and weight were analyzed over time from 1964 to 1972 among health examination participants who had been exposed before the age of 10 years old (aged 20 to 35 years at the time of physical measurements). The results showed decreased height and weight with increasing radiation dose (DS86).[51]

Subsequently, radiation effects on changes in height were analyzed from 1958 to 1998 in approximately 12,000 health examination participants (average 9.3 measurements per person), regardless of age at the time of exposure.[52] In both male and female survivors who were exposed before the age of 19 years old, height loss was observed after they had reached the age of 20, when physical growth is complete. The dose effect of radiation exposure was found to be greater in women than in men and in individuals who were younger at exposure. The height loss per 1 Gy for those exposed at the age of 0 years old was estimated to be -1.2 cm for men and -2.0 cm for women. For those exposed at the age of 10 years old, the respective estimated height loss per 1 Gy was -0.57 cm and -0.96 cm. Besides radiation, physical growth can also be affected by malnutrition, psychological disturbances such as stress, and social and economic hardship. It should be noted that the contribution of these factors cannot be assessed due to a lack of data on these factors in this case.

The effect on aging-related bone diseases has also been investigated. The incidence of thoracic vertebral fractures was analyzed based on the interpretation of lateral chest X-rays from approximately 15,000 individuals taken between 1958 and 1986, with no effect found from exposure to atomic bomb radiation.[53] Such analyses examined not only radiation effects but also effects of age at the time of X-ray measurements, sex, year of birth, city of residence, and other characteristics in the Japanese study population.

column Activities Related to Continuing Studies

The Department of Clinical Studies conducts health examinations on atomic bomb survivors and their children to assess health effects of radiation exposure. To ensure our research continues over the long term while also maintaining study quality, it is essential that participants can cooperate in our studies with peace of mind. RERF adopts a variety of measures to build and maintain relationships of trust with participants to help them maintain their health and alleviate their health concerns.

Considerations during health examinations

1. The timing and date of health examinations are arranged to accommodate examinees' needs and ensure the cooperation of as many participants as possible.
   Regular health examinations are conducted during the day but, for working individuals, exams are also regularly offered on Saturdays and in the evenings.
   To ensure that study participants can participate in the health examinations with peace of mind, RERF contacts participants the day before the scheduled exam to confirm their health status. Accommodations are also made for sudden scheduling changes.
   Additionally, the facility is barrier-free to ensure accessibility for wheelchair users.
2. Prior to health examinations, staff carefully explain the purpose of the study and details of the examinations to facilitate participants' understanding and obtain their consent.
3. Once the health examinations have been completed, a report of the results is promptly sent to examinees. RERF aims to make the report readily understandable and not overly technical.
   If lifestyle changes, such as diet or exercise, are necessary based on the health examination results, a public health nurse is ready to provide health and lifestyle advice by telephone or mail.
4. RERF reports the health examination results to a family physician as needed. Consultations are also provided to individuals without a primary care physician, and if more detailed examinations are required, RERF refers them to a general hospital through its Regional Liaison Office.

Consultations regarding health and radiation effects

Specialized staff, including physicians, public health nurses, and nurses, are available to answer questions about health issues and associations between radiation and illness.

Providing information through leaflets

RERF regularly distributes leaflets to provide information on disease prevention, health maintenance, and radiation effects, as well as to report research results.

The Hiroshima Laboratory and the Nagasaki Laboratory publish their own newsletters annually: *Kenko no Mori* (in English, 'Health Forest') and *Health Note: Kane* ('Health Note: Bell'), respectively.

B. Studies of In Utero Survivors

Death and cancer incidence

For 2,463 in-utero survivors (1,214 males and 1,249 females), the effects of A-bomb radiation exposure on mortality rates from solid cancers, noncancer diseases, and external causes between the ages of four and 62, were investigated from 1950 through 2012.[54] In males, an effect of A-bomb radiation exposure on noncancer disease mortality was observed (excess relative risk [ERR] 1.22/Gy), but no effect was observed on solid cancer mortality or external cause mortality. In females, the effects of A-bomb radiation exposure were observed on mortality from solid cancers (ERR 2.24/Gy), noncancer diseases (ERR 2.86/Gy), and external causes such as accidents and suicide (ERR 2.57/Gy). In risk analysis, maternal uterine radiation dose is used as a surrogate measure for fetal radiation dose. For the effect of A-bomb radiation exposure on mortality in adulthood, it is necessary to take into account the study participants' health condition and environment during gestation and childhood. We therefore examined the health status and family size of the participants at the time of birth using information obtained from interviews and mail surveys conducted through the 1960s. The results showed that small head circumference, low birth weight, and the death of one or both parents were associated with A-bomb radiation exposure dose, and that these factors were also associated with mortality risk in adulthood for in-utero survivors. Therefore, the association between A-bomb radiation exposure and death observed in the in-utero survivors is likely mediated by many A-bomb-related factors and should be interpreted with caution, taking into account these factors.

A comparison of cancer incidence data in the age range of 12–55 years among in-utero survivors and survivors exposed during childhood (up to age five at exposure) was also made.[55] For in utero survivors, the excess relative risk per 1 Gy (ERR/Gy) of A-bomb radiation at age 50 was 1.0, with a significant dose-response relationship observed. Although this value is lower than that for those exposed during childhood (ERR 1.7/Gy), there was no statistically significant difference in the excess relative risk between the two groups. While excess absolute rate increased rapidly with age among those exposed during childhood, no increase with age was observed in in-utero survivors. At present, no statistically significant difference has been observed in the absolute excess rate between the two groups. Based on these results, the risk of cancer incidence in adulthood due to A-bomb radiation exposure during gestation appears to at least be no greater than the effects of A-bomb radiation exposure during childhood.

Noncancer diseases during adulthood

For in utero survivors, who have been included in the AHS biennial health examination program since 1978, several studies have been conducted to investigate the effects of radiation exposure on the risk of non-cancer diseases after adulthood and the results have been reported. In a study[56] conducted between 2000 and 2003 on 319 in-utero survivors for whom radiation dose was estimated, no clear effect of radiation exposure on the prevalence of thyroid nodules or autoimmune thyroid disease was observed. An ophthalmologic study[57] conducted on 143 in-utero survivors between 2000 and 2002 found no clear dose effect on cataract prevalence. Furthermore, an analysis[58] conducted on 506 in-utero survivors found no clear dose effects of radiation exposure on the incidence of hypertension, hypercholesterolemia, and cardiovascular diseases (stroke and myocardial infarction) between 1978 and 2003. However, in these studies, the in-utero survivors were relatively young (less than 60 years old) and had not yet reached the age at which these diseases commonly occur. Therefore, further investigation is considered necessary.

C. Study of the Children (F_1 Offspring) of A-Bomb Survivors

Death, cancer incidence

In studies of cancer incidence in the children of A-bomb survivors (second-generation A-bomb survivors), an analysis of childhood leukemia and early-onset solid cancers in one of the early follow-up studies found no association between parental radiation exposure and the onset of cancer up to age 20 years[59] or between the ages of 20 and 40. Furthermore, the latest analysis by Izumi et al., in a follow-up until 1997, found no effects of parental radiation exposure on the incidence of leukemia, lymphoma, or solid cancers in individuals under the age of 20, or between the ages of 20 and 40.[60] However, the incidence of cancers (mainly solid cancers) that occur in and after adulthood had only just begun to increase in the study population, so it is too early to make a definitive judgment, with further investigation needed in the future.

In mortality studies, no effects of parental radiation exposure have been observed in individuals up to and including the age of 15 years,[61] under the age of 20,[62] or after and including the age of 20 (average age 46 years old).[63]

The latest analysis by Grant et al. found no effects of parental exposure in a follow-up until 2009.[64] Compared with children whose fathers received 0 mGy, there was no significant increase in cancer mortality in children whose fathers were exposed to 1–49 mGy, 50–149 mGy, 150–499 mGy, or ≥500 mGy (Figure 4). In addition, no significant increase in mortality has been observed in comparisons based on maternal radiation dose. No effect of parental radiation exposure has been observed in deaths either before or after age 20 years. Similar comparisons in noncancer diseases found no significant increase in mortality. However, because analyses were performed at a time when the mortality percentage was less than 10% of the total study population and many of the participants were still young (mean age 53 years as of 2009), it is difficult to conclude there was no effect of parental radiation exposure, making continued follow-up study necessary in the future.

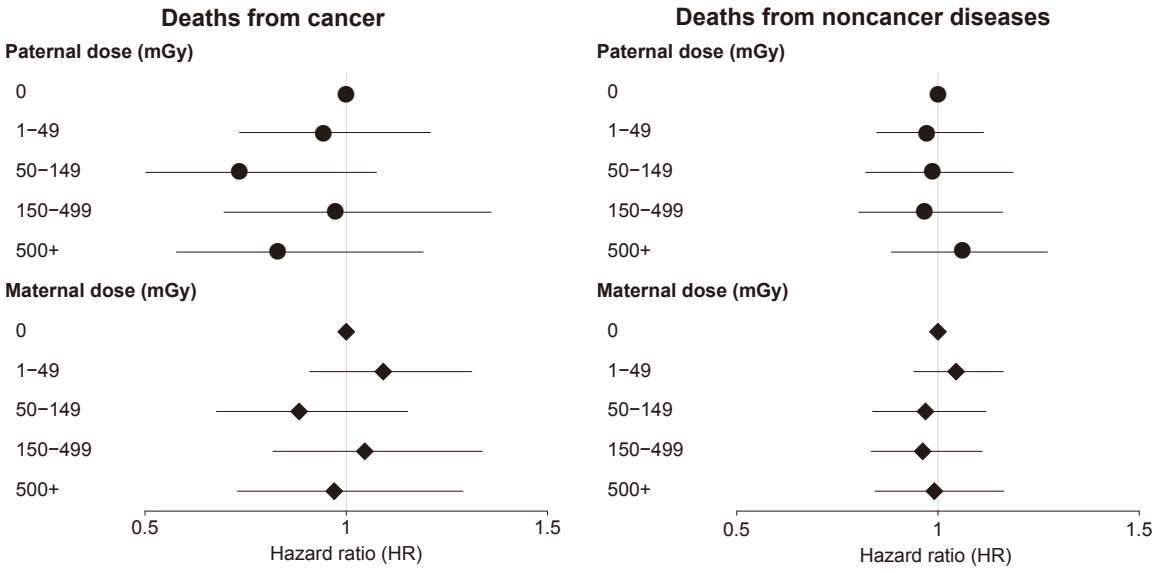


Figure 4. Parental radiation dose and child mortality risk (born in 1946–1984, follow-up period until 2009)[64]. The horizontal bars indicate 95% confidence intervals.

Clinical studies

For the offspring of A-bomb survivors, clinical research after the age of one year had not been conducted. Since many multifactorial diseases (diseases caused by a combination of lifestyle factors, environmental factors, and genetic factors) occur after adulthood, a research plan was designed to investigate the heritable effects of radiation exposure on multifactorial diseases. Based on the research plan, the Health Effects Study of the Children of A-bomb Survivors was conducted between 2000 and 2006 using mail surveys and clinical studies. In the clinical studies, interviews about medical history and lifestyle habits, as well as health examinations that included blood pressure measurements, electrocardiograms, and blood tests were performed, similarly to those conducted in the Adult Health Study (AHS) of A-bomb survivors. As of the end of September 2006, a total of 11,951 offspring of A-bomb survivors in Hiroshima and Nagasaki (5,702 males and 6,249 females) had undergone health examinations. The mean age of the participants was 48.6 years, with 54% of the study population in their 50s. Studies[65,66] were conducted on these health examination participants to examine the association between parental radiation exposure and prevalence of multifactorial diseases occurring in adulthood. The multifactorial diseases analyzed were hypertension (26.4%), hypercholesterolemia (38.7%), diabetes mellitus (6.4%), myocardial infarction (0.4%), angina pectoris (0.8%), and stroke (0.7%) (figures in parentheses indicate prevalence in all participants). An analysis[65] was conducted to investigate the association between parental radiation exposure and the presence of one or more of the six diseases studied, defined as "having a multifactorial disease."

The analysis found no clear relationship between parental radiation exposure and the prevalence of multifactorial diseases in their offspring, for either paternal or maternal doses. These results were not affected by parents' age at exposure, period from exposure to conception (birth), or parents' medical history of multifactorial diseases. While an analysis by the offspring's sex revealed a negative association between paternal radiation dose and the prevalence of multifactorial diseases in male offspring, it is unclear whether such results are biologically meaningful or the result of bias related to the decision to participate in the study, and therefore the results should be interpreted with caution. Analyses[66] were also conducted to examine the association between parental radiation dose and each of the six diseases studied, conjoint dose (the sum of paternal and maternal dose). No evidence was found that any parental radiation exposure increased the prevalence of multifactorial diseases in offspring. Further, an analysis by sex suggested a negative association between the prevalence of hypercholesterolemia or diabetes mellitus and paternal dose in male offspring of A-bomb survivors. Since no statistically clear sex differences in the effects of radiation exposure were found, further observation is needed.

In the 2002–2006 study, the offspring of A-bomb survivors were still relatively young, just entering the age at which multifactorial diseases tend to occur. In addition, the presence of biases associated with a prevalence study cannot be ruled out. Therefore, RERF has been conducting an incidence study based on health examinations in four-year cycles since 2010. The study is currently being analyzed, and results are expected in the near future.

Cytogenetic study

Extensive chromosomal analyses have been conducted on blood lymphocytes from the children of A-bomb survivors (1967–1985) to investigate whether stable chromosomal abnormalities caused by radiation exposure in parental germ cells are inherited by their children. Chromosomal aberrations in blood lymphocytes were compared between 8,322 children having one or both parents exposed within 2,000 meters of the hypocenter (estimated dose ≥0.01 Gy) and 7,976 children with both parents exposed beyond 2,500 meters (estimated dose <0.01 Gy) or not in city at the time of the bombings.[67] Stable chromosomal

aberrations were detected in 18 children in the former group and 25 children in the latter group, providing no evidence that parental radiation exposure increased the proportion of children with aberrations. Subsequent testing of the parents and siblings revealed that the majority of stable chromosomal aberrations were not of a de novo variety, but rather aberrations inherited from one of the parents. Furthermore, de novo chromosomal aberrations were detected in one case each of the exposed group and the control group, with no difference in observed incidence.

Biochemical genetic study (blood protein mutations)

In this study, 30 types of blood proteins were examined for mutations using one-dimensional electrophoresis or reduced enzyme activity. In 1976, biochemical mutation analysis was state-of-the-art technology because protein mass spectrometry and DNA fragment amplification (PCR) to decode base sequences were not yet available. Over a 10-year period, a total of approximately 24,000 children of A-bomb survivors of the Life Span Study (LSS) population and children of unexposed parents were screened for mutations by electrophoresis, and approximately 10,000 of that number were screened based on decreased enzyme activity.[68-70] The electrophoresis examinations detected mutations in two children whose parents were exposed to a total radiation dose of ≥0.01 Gy (exposed group) and three children whose parents received <0.01 Gy (control group).[68, 69] The screening based on decreased enzyme activity detected mutations in only one child in the exposed group. Overall, these protein-level studies showed no significant difference in mutation rates between the exposed and control groups.[70]

DNA studies

Before advances in DNA sequencing technology, a large volume of DNA was required to detect mutations in DNA fragments. For that purpose, a large amount of DNA was extracted from cell lines established with B lymphocytes to investigate mutations. Cell lines were generated from the blood cells of a portion of the parents and all available children of 1,000 families, 500 with one or both parents exposed to doses of ≥0.01 Gy and 500 with neither parent exposed to significant doses.

Pilot studies have been conducted using DNA from 100 families, 50 with only one parent exposed to ≥0.5 Gy of radiation and 50 controls with unexposed parents, to examine mutations in short tandem repeats (STR) and to conduct mutation studies using DNA two-dimensional electrophoresis and microarrays.[71-74] STRs, which exist in large numbers in the human genome, are repetitive sequences of short DNA motifs. The number of repeats is genetically determined, but it is relatively common for the number of repeats to differ between parents and children because of naturally occurring mutations. Such STRs are known to include microsatellites, where 1–5 base pairs repeat as a unit, and minisatellites, where 6–100 base pairs repeat. Mutations in eight blocks of minisatellites were examined in 61 children from the exposed group (mean radiation dose 1.47 Gy), 58 children from the control group, and their parents. The proportion of participants with mutations in the number of repeats was 2.6% in the exposed group and 2.8% in the control group.[71] Examination of 40 microsatellite loci revealed mutations in 0.39% of 66 exposed families (mean radiation dose 1.56 Gy) and in 0.35% of 63 control families,[72] suggesting no effect of parental radiation exposure on the inheritance of STR.

Hypothesizing that deletion mutations, which often occur after radiation exposure, could be detected with DNA two-dimensional electrophoresis, RERF analyzed 62 children from 50 control families and 66 children from 50 exposed families (mean radiation dose 1.7 Gy) and their parents. Only one deletion mutation was detected among 56,176 loci examined in the control group, and no deletion mutations were detected among 59,942 loci examined in the exposed group.[73]

A preliminary study was also conducted to determine copy number variations (CNVs)

in DNA fragments using microarray-based comparative genomic hybridization (CGH). In the microarray-based CGH, approximately 2,500 DNA clones (called PACs or BACs) were used as probes. The result of CGH analysis of 40 children from the exposed group and 40 children from the control group confirmed that all 251 copy number variations detected already existed in the parents, with none of them being new, de novo variations in the children.[74]

The results of the genetic studies conducted to date are summarized in Table 2.

Table 2. Results of genetic studies to date

Study item	Number of families (number of children)		Effects of radiation exposure
	Exposed	Control	
Chromosomal aberrations	8, 322	7, 976	Not significant
Protein electrophoresis	11, 364	12, 297	Not significant
Enzyme activity	4, 989	5, 026	Not significant
Microsatellite	50	50	Not significant
Minisatellite	61	58	Not significant
DNA two-dimensional electrophoresis	50	50	Not significant
DNA fragment CNV	40	40	Not significant

Whole-genome study

Technology is now available that can analyze the effects of radiation exposure on DNA at the whole genome level, and a new study involving whole genome sequencing (WGS) of approximately 600 families is underway. Families included in the study were selected based on previous cytogenetic studies (analysis of chromosomal aberrations), using a "Trio" statistical design, with each trio consisting of a child and two parents. It is anticipated that more detailed findings pertaining to the genetic effects of A-bomb radiation will be obtained in the near future.

D. Radiation Dosimetry and its Application to Studies

Physical dosimetry

Over the years, methodology for estimating the radiation dose received by atomic bomb survivors has continuously improved. After the Tentative 1957 Dosimetry System (T57D) was developed as an initial simplified method, the Tentative 1965 Dosimetry System (T65D) was established as a more comprehensive system and widely used for risk determination until the late 1970s. However, T65D dose estimates were based on measurements only within 1 km of the hypocenter, which led to discrepancies when compared with measurements from tiles and roof tiles exposed beyond that distance in Hiroshima and Nagasaki. As a result, doses were reassessed.

The Dosimetry System 1986 (DS86) introduced large-scale computer simulations to estimate radiation doses, incorporating the effects of shielding by buildings and the human body for both gamma and neutron radiation. The system provided dose estimates for 15 separate organs at the individual level.[75] Following the introduction of DS86, discrepancies were noted between measured values of neutron-induced radioactivity and DS86 calculations, particularly beyond 1.5 km from the Hiroshima hypocenter.[75] This issue was resolved by increasing the assumed detonation altitude by 20 meters. This adjustment plus further refinements led to the development of Dosimetry System 2002 (DS02).[76] DS02 represents a highly advanced dosimetry system with no equivalent worldwide. However, it was noted that distortions in historical maps and truncation of decimal places in coordinate data affected the accuracy of input data for survivor locations. These issues were subsequently addressed, leading to the recalculation of dose estimates under DS02R1.[77] The dose estimates obtained using DS02R1 are considered to have smaller errors compared to previous dose estimates. However, the systematic effects are relatively minor. It has been confirmed that these differences do not significantly impact the results of epidemiological studies.

The organ dose estimation models used in DS86 were based on three simplified anatomical models corresponding to different age groups: infants (9.7 kg), children aged 3–12 years (19.8 kg), and individuals aged 12 years or older (55

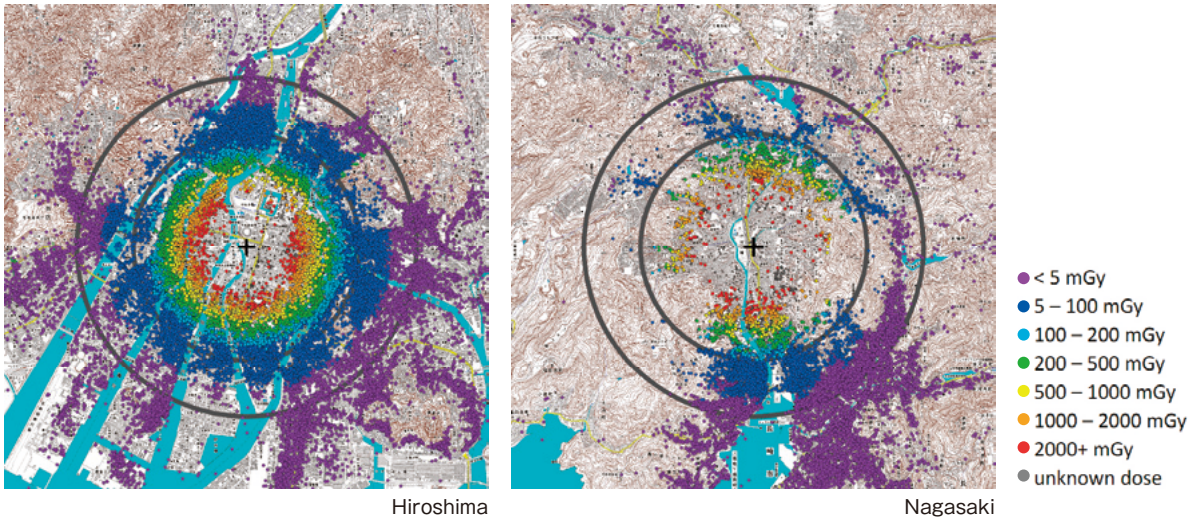


Figure 5. Dose distribution of atomic bomb survivors in the LSS cohort

Each point represents the location and estimated dose of 93,741 survivors exposed to radiation, excluding those who were residing outside the city at the time of the bombing, from a total of 120,321 individuals in the LSS cohort. The cross in the figure indicates the hypocenter, and the circles indicate distances of 2 km and 3 km from the hypocenter, respectively.

kg). However, these models were considered overly simplified in terms of human shape and anatomy. Since DS02, there has been increasing demand for additional organ availability, greater precision in organ dose estimates, and greater anatomical detail.

Starting in 2018, an international working group implemented organ dose estimation using state-of-the-art computational phantoms (J45) that incorporate sex-specific and age-specific anatomical models. These modern phantoms are expected to enhance the accuracy of organ dose estimates, and an updated set of organ doses based on DS02R1 is scheduled to be introduced in 2025.[78, 79]

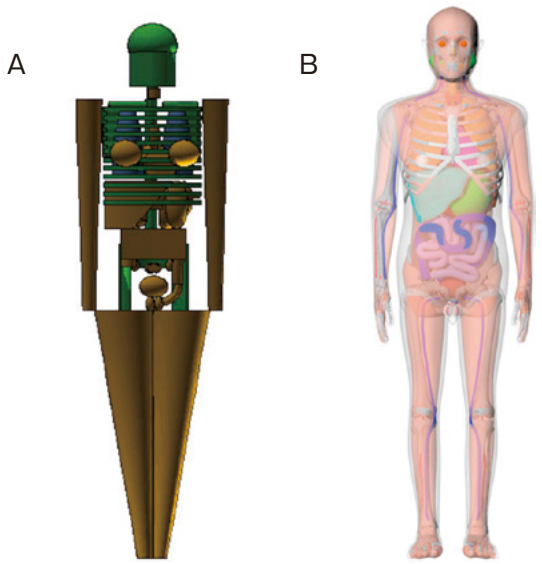


Figure 6. (A) A three-dimensional rendering of the DS86/DS02 adult male phantom, with the trunk and head/neck made transparent. (B) The J45 phantom, a computational model replicating the body shape of a Japanese adult male in 1945.

Radiation dosimetry errors and risk estimation

Effects of radiation exposure on the risk of new cases (incidence) or death (mortality) from disease or mortality are estimated using a measure called relative risk, which here represents how many times higher the risk is in an exposed population compared with an unexposed population, and incidence rate (or mortality rate), which represents the portion of increase in incidence (or mortality) that can be attributed to radiation exposure. These parameters are estimated using statistical models that take into account factors other than dose that might affect disease incidence or mortality. The Life Span Study (LSS) has been used to estimate excess risk by assuming a dose-response relationship for the increase attributable to radiation, both in terms of relative risk and portion of rate increase.

[Excess relative risk (ERR) model]

Incidence rate (mortality rate) =
[Incidence (mortality) in unexposed population]
× [1 + excess risk from radiation]

[Excess absolute rate (EAR) model]

Incidence rate (mortality rate) =
[Incidence (mortality) in unexposed population]
+ [excess rate from radiation]

The ERR represents how many times the risk of disease incidence or mortality has increased due to radiation exposure, while EAR represents the increase in rates of incidence or mortality (in absolute terms). Both values in excess of zero indicate an increase in risk due to radiation exposure.

In statistical models, the association between radiation and risk is expressed as a function of radiation dose, allowing estimation of the dose-response relationship. However, it is well recognized that risk estimates might not be accurate if there are errors in radiation dose estimates. The DS86 and later radiation dosimetry systems are based on physical simulations using computers. With that, errors in radiation dosimetry, including errors in the simulations, were examined. Statistical methods were developed to correct for the effects of errors in the radiation dose estimates. Since then, the methods have been used in all RERF studies to ensure accurate estimation of the association between atomic bomb radiation and risk.[80] There are thought to be two types of errors in radiation dosimetry: random errors and averaging errors. Random errors arise from uncertainty in data regarding survivor location, information that is based on memory at the time of the bombing and other factors,

resulting partly from the long interval between exposure and the study. The degree of error in information about distance from the hypocenter has long been studied.[81] Meanwhile, averaging errors occur in such instances as when the radiation dosimetry system tentatively assigns a mean shielding value to study participants lacking detailed data on shielding conditions at the time of exposure to estimate radiation effects. To date, RERF research has not taken into account such averaging errors but, in recent years, a correction method has been proposed to account for the two types of errors.[82,83] In addition, work on development of statistical methods to obtain more accurate estimates of radiation effects is ongoing.

Biological dose estimation

Chromosomal aberrations

The first chromosome survey that began in 1966 targeted unstable aberrations (such as dicentric chromosomes) because they are easy to detect. However, because they have a half-life of only a few years, they were rarely observed. Therefore, subsequent research focused on stable aberrations (such as translocations), which are more difficult to identify but are considered to remain largely unchanged over time. From 1966 to 1993, a study on the frequency of stable chromosomal aberrations was conducted using the Giemsa staining method, gathering data from around 3,000 atomic bomb survivors in Hiroshima and Nagasaki.

The findings included:

(1) Stable chromosomal aberrations persist in the peripheral blood T lymphocytes of survivors even several decades after exposure; (2) the proportion of cells with chromosomal aberrations increases with radiation dose; (3) the frequency of chromosomal aberrations varies greatly among subjects assigned the same physical dose; (4) the dose-response gradient for chromosomal aberrations is steeper in Nagasaki survivors than in Hiroshima survivors; (5) the dose-response gradient varies depending on the shielding conditions of survivors.[84]

In 1993, the Giemsa method for detecting chromosomal aberrations was replaced with fluorescence in situ hybridization (FISH), a more accurate method. Additionally, whereas the Giemsa method had been conducted separately in Hiroshima and Nagasaki, the

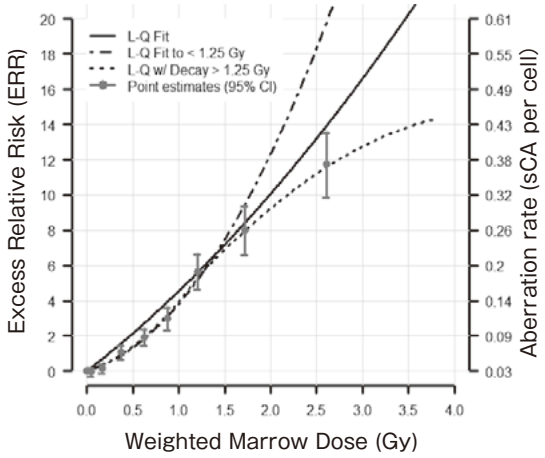


Figure 7. Dose-response curve for chromosomal aberrations. The left vertical axis represents excess relative risk (ERR), while the right vertical axis represents the corresponding chromosomal aberration frequency for a 70-year-old male survivor in Hiroshima at the time of blood collection.

L-Q: Linear-quadratic model; L-Qw/Decay>1.25 Gy: a model assuming a decreasing trend above 1.25 Gy based on a linear quadratic model. ● indicates the published ERR estimates corresponding to each dose category. (Source: Radiation Research Society)

FISH analysis was centralized in the Hiroshima laboratory. The FISH results confirmed the same association between chromosomal aberration frequency and physical dose as was observed with the Giemsa method. However, the city-to-city difference previously observed in point (4) became significantly smaller, suggesting that the difference in aberration detection ability between the Hiroshima and Nagasaki laboratories may have contributed to the observed city difference.[85]

Using data obtained from the FISH method, it became possible to convert chromosomal aberration frequency into γ-ray dose and compare it with DS02R1 dose estimates. This comparison confirmed that the radiation dose estimates for atomic bomb survivors used in RERF studies are highly accurate.[86]

Electron spin resonance (ESR) method using tooth enamel

By collecting extracted teeth that were removed for medical reasons and isolating the enamel, the amount of radiation-induced molecular radicals can be measured using electron spin resonance (ESR) or electron paramagnetic resonance (EPR). The intensity of the ESR signal is proportional to the amount of radiation exposure. Using teeth from 60 atomic bomb survivors, a comparison was made between estimated doses derived from molars using ESR and the frequency of translocations in lymphocytes from the same individuals (Figure 8).[87] The results showed closely matched dose-response curves, providing further validation of biological dosimetry methods.

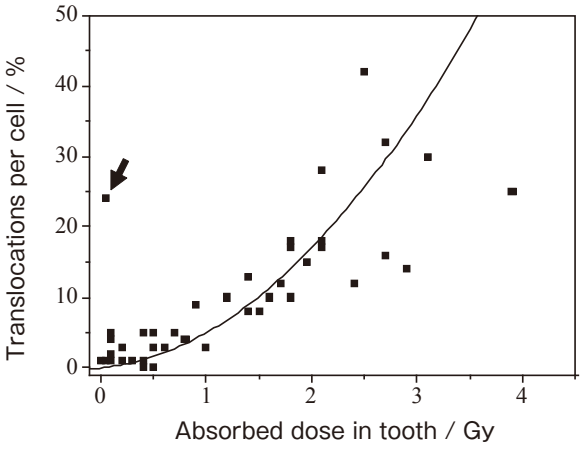


Figure 8. Estimated radiation dose to the molar and translocation frequency in lymphocytes of the same individual

The curve represents the dose–response relationship for dicentric chromosomes obtained from in vitro γ-ray irradiation experiments on lymphocytes (it is assumed that dicentric chromosomes and translocations occur at the same frequency). The arrow in the figure indicates a wisdom tooth (third molar) from an individual exposed at the age of 15 years, and since the enamel had not yet formed at the time of exposure, the absorbed dose in that tooth is estimated to be 0 Gy (there is considerable individual variation in the timing of wisdom tooth development).

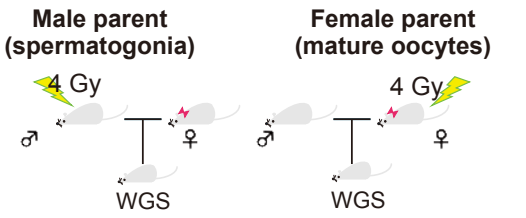
E. Molecular Biology Research

Molecular genetics

The genetic effects of radiation exposure are of great interest to both the scientific community and the general public. A comprehensive understanding of radiation's genetic effects in humans requires not only epidemiological and clinical studies of the children of atomic bomb survivors but also research at the molecular (genetic and epigenetic) level.

Preliminary study in mouse model

Molecular genetics research has established a method for investigating the genetic effects of radiation in a mouse model using the latest DNA sequencing technology. This method enables the identification of genomic mutations inherited by children from either the paternal or maternal germ (reproductive) cells, classifying them into single nucleotide variants (SNVs), insertions/deletions (Indels), multisite mutations (MSMs), and structural variants (SVs) (Figure 9).



	No. of offspring	No. of mutations			
		SNV	Indel	MSM	SV
Unirradiated	6	62	6	1	3
Irradiated male	6	65	36	10	Not analyzed
Irradiated female	6	55	22	10	5

Created from data by Satoh, *Sci Rep* 2020

Figure 9. Results of preliminary study in mice

The table in Figure 9 shows transgenerational mutations detected in offspring produced by mating male and female mice after either parent was exposed to 4 Gy of radiation. Radiation-induced transgenerational mutations were characterized by Indels and MSMs (in red), with non-repetitive Indels specifically induced.[88]

Studies of transgenerational genomic effects of exposure to A-bomb radiation

To determine the effects of atomic bomb exposure in children, RERF has collected blood samples from atomic bomb survivors, their spouses, and their children (the second generation) since 1985. RERF is now planning to investigate DNA changes occurring in the children of A-bomb survivors by sequencing genomic DNA from approximately 600 families comprised of survivor parents and their children (Figure 10). Also investigated will be whether observed DNA changes are inherited from either the paternal or maternal germ (reproductive) cells.

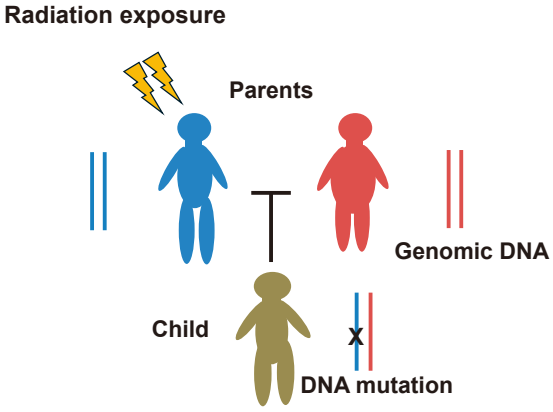


Figure 10. Transgenerational genomic mutations

Studies on the genetic effects of atomic bomb exposure must be conducted only after gaining the full understanding of A-bomb survivors, their children, and civil society, given that genetic effects of A-bomb exposure involve social issues. Furthermore, since the analysis of an individual's entire genome could reveal changes in disease-related DNA, careful ethical consideration must be paid to the issue of how to explain the results. RERF has extensively consulted Japanese and international specialists in human genome analysis and medical research ethics to advise on ethical aspects of genome sequencing analysis of A-bomb survivors and their spouses and children. RERF is conducting molecular genetics research

into the effects of radiation exposure while maintaining transparent communication with the A-bomb survivors, spouses, and children who participate in our studies, the media, and the general public. In 2024, a series of public lectures was held in Hiroshima and Nagasaki titled “Parental Exposure to Atomic Bombing and Their Children’s Health” to widely solicit opinions and promote understanding of molecular genetics research into the genetic effects of radiation exposure.

In recent years, molecular genetic techniques have become useful for elucidating the molecular mechanisms of radiation effects. RERF is not only investigating the genetic effects of radiation exposure but also collaborating with research institutes in Japan and overseas to apply cutting-edge, whole-genome sequencing (WGS) techniques and promote innovative radiation biology research.

Cellular genomics

In utero exposure

Chromosome analysis has been used not only to estimate biological radiation exposure doses (p. 38), but also as a tool to investigate radiation effects on the living body, particularly the hematopoietic system. In a study of survivors exposed in utero (Figure 11), the frequency of stable chromosome aberrations in blood T lymphocytes was lower than that of their mothers, with no significant association with radiation dose.[89] A similar low frequency of chromosome aberrations possibly due to in utero exposure was also observed in a study of pregnant mice.[90] These results suggest that the effects of in utero exposure on the hematopoietic system may not significantly manifest after birth. This may reflect the fact that cells responsible for establishing the hematopoietic system during fetal development are not significantly involved in the production of T lymphocytes after birth.

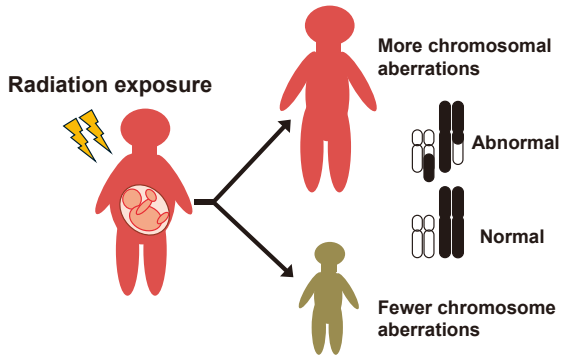


Figure 11. Chromosome aberrations in children exposed in utero and their mothers

On the other hand, animal experiments have shown that the frequency of chromosomal aberrations in thyroid and mammary gland cells due to in utero exposure is comparable to that observed in mothers exposed as adults.[91,92] Taken together, differential organogenesis during the fetal period may determine whether chromosome aberrations induced in utero exposure (i.e., radiation-induced genome damage) persist in organ cells after birth.

Clonal chromosome aberrations

A blood cell population with identical chromosomal aberrations (clonal chromosome aberrations) can arise from the extensive proliferation of a single precursor cell carrying the same chromosomal aberrations. A high frequency of such populations (in blue) was found in atomic bomb survivors exposed to high doses (Table 3).[93]

Table 3. Clones with the same chromosomal aberration frequency (in blue) in high-dose A-bomb survivors

Frequency of chromosomal aberrations	No. of survivors examined	No. of abnormal clones	No. of survivors with abnormal clones
0	6	0	0
0–0. 1	427	29	26
0. 1–0. 2	61	32	20
>0. 2	19	35	15
Total	513	96	61

Somatic mutations

We have previously shown in A-bomb survivors that the frequency of mutant cells depends on radiation exposure dose, as demonstrated using the glycophorin A (*GPA*) gene in erythrocytes[94] and the hypoxanthine-guanine phosphoribosyl transferase (*HPRT*) gene in T lymphocytes.[95] More recently,

advanced sequencing techniques have become available to identify mutations throughout the whole cell genome (Figure 12).

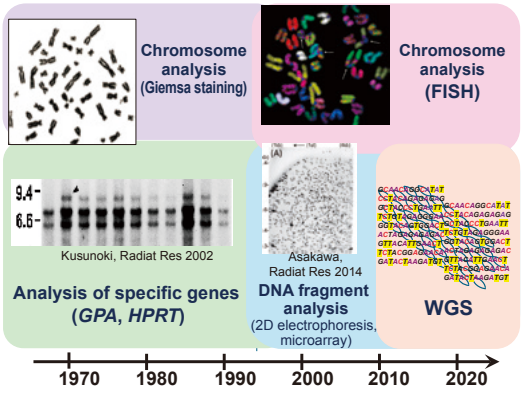


Figure 12. History of somatic mutation analysis at RERF

In mouse experiments, bone marrow hematopoietic cells are used to identify DNA mutations in cells exposed to high radiation doses using whole-exome sequencing (WES) and WGS technologies. These state-of-the-art technologies are used not only to investigate the genetic effects of the atomic bomb but also to analyze the blood cell genomes of A-bomb survivors, aiming to comprehensively analyze radiation-induced genomic mutations and to examine such mutations by incorporating the timeframe of development and radiation-specific mutation types.

To date, results of WGS performed on in vitro cultured colonies derived from single hematopoietic stem cells of high-dose irradiated mice suggest that non-repeat deletions may be characteristic of radiation-induced DNA mutations (Figure 13).[96] RERF is currently investigating whether a similar method can be used in the whole-genome analysis of human hematopoietic stem cells, with the aim of applying this technology to a comprehensive analysis of genomic mutations in preserved blood samples from A-bomb survivors.

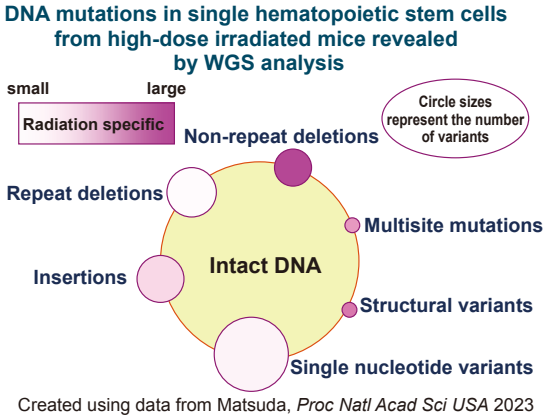


Figure 13. Whole-genome analysis of mouse hematopoietic stem cells

Genome damage repair

Chromosome aberrations and somatic mutations result from errors in DNA damage repair. In an experiment involving irradiation of cultured human cells in vitro, however, quite a few cells remained alive despite halted DNA repair. Chromodomain helicase DNA binding protein 7 (CHD7) was identified as one of the proteins that accumulated around the damaged DNA site in such cells.[97] Interestingly, CHD7 plays an important role in the morphogenesis of neurosensory organs. If substantial DNA damage remains unrepaired, the malformation of neurosensory organs could occur (Figure 14).

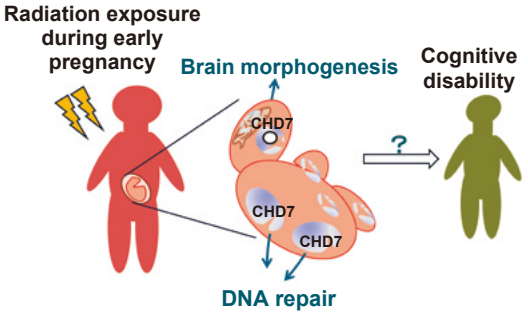


Figure 14. Genome damage and abnormal brain morphogenesis

Radiation exposure during early fetal development can induce brain malformation. This could be explained by the assumption that CHD7 is deficient during that stage of development due to its extensive use in repairing large amounts of DNA damage.

Hematopoietic and immune systems

Studies on the biological effects of A-bomb radiation have mainly used blood samples donated by participants of the Adult Health Study (AHS). Consequently, molecular biological studies have largely focused on the hematopoietic and immune

systems. Chromosomal aberrations and somatic mutations have been detected in T lymphocytes, which play a central role in cellular immunity, as well as in hematopoietic progenitor cells in a radiation dose-dependent manner. Changes in erythrocyte indices and increases in leukocyte count due to radiation exposure have also been observed in blood cell measurements in the AHS. These findings suggest that radiation-induced damage to the hematopoietic and immune systems might be in part associated with the onset of leukemia and other diseases commonly observed among A-bomb survivors.

Clonal hematopoiesis

No correlation has been found between radiation exposure and the number of hematopoietic progenitor cells in the blood or their proliferation or differentiation function in vitro. However, in recent years, clonal hematopoiesis, defined as the clonal proliferation of blood cells with somatic mutations, has often been observed in the healthy elderly, and it is suggested that individuals with clonal hematopoiesis have a high risk of malignant blood diseases, such as leukemia, and inflammatory diseases, such as cardiovascular disease and hepatitis (Figure 15).

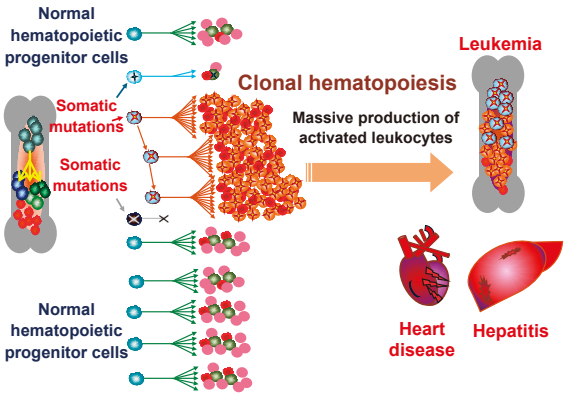


Figure 15. Clonal hematopoiesis and disease

Somatic mutations[94, 95] and/or chromosomal aberrations[93] were observed at a higher frequency in blood cells from high-dose A-bomb survivors. This finding suggests that clonal hematopoiesis might occur more frequently in this population than in unexposed individuals. Research is ongoing to detect clonal hematopoiesis through WES analysis of preserved blood samples from A-bomb survivors. RERF research has found that clonal hematopoiesis occurs at a high frequency in mice irradiated with 3 Gy of X-rays.[98] Furthermore, mouse experiments have revealed characteristics of radiation-induced clonal hematopoiesis, such as increased neutrophils and other inflammatory myeloid cells, as well as the expansion of mutant cell clones. With advances in the analysis of blood cells from A-bomb survivors, RERF is expected to gain insight into understanding the mechanism by which radiation-induced clonal hematopoiesis leads to the development of certain radiation-related diseases.

Immunity

Leukocytes play a major role in immunity. Among such cells, various subsets of T lymphocytes, each with distinct properties and functions, play a central role in controlling inflammation and defending against pathogens and cancer cells. RERF has performed flow cytometry (Table 4) and in vitro functional analyses of lymphocytes, primarily T cells.[99-102] The results showed a radiation dose-dependent

Table 4. Changes in blood lymphocytes due to atomic bomb radiation (changes per 1 Gy)

Lymphocytes	Change (%) due to radiation exposure	Study period (number of individuals studied)
T lymphocytes All CD^{+4} cells	Decreased (2.0%)	1992–95 (723)
Naïve	Decreased (4.5%)	1992–95 (723)
Memory	Unchanged	1992–95 (723)
Th1	Increased (2.7%)	2000–02 (3,511)
Th2	Increased (3.5%)	2000–02 (3,511)
Regulatory T	Increased (2.7%)	2006–08 (1,035)
All $CD8^{+}$ cells	Unchanged	1992–95 (723)
Naïve	Decreased (8.4%)	2000–03 (533)
Memory (Tcm)	Increased (11.5%)	2000–03 (533)
Memory (Tem)	Increased (7.8%)	2000–03 (533)
B lymphocytes	Increased (8.5%)	1988–92 (411)
NK lymphocytes	Unchanged	1988–92 (411)

decrease in the proportions of CD4 and CD8 T lymphocyte subsets and naïve T lymphocytes, whereas the proportion of memory T lymphocytes increased dependent on radiation dose. In addition, the proportion of regulatory T lymphocytes, which act as immune response suppressors, increased in a radiation-dose-dependent manner. B lymphocytes significantly increased with radiation exposure (Table 4), while NK lymphocytes remained unchanged. These proportions of T lymphocyte subsets appear to be associated with impaired T lymphocyte function, as demonstrated in vitro by decreased proliferative response to mitogens and interleukin-2 (IL-2) production.[101]

Such changes in T lymphocyte subsets, including increased levels of Th1 and Th2 CD4 T lymphocytes,[102] might also be associated with increased production of inflammatory cytokines, such as interferon gamma (IFN-γ), tumor necrosis factor-α (TNF-α), IL-6, and IL-10, as well as in increased levels of inflammatory markers, such as CRP, erythrocyte sedimentation rate (ESR), and blood and intracellular reactive oxygen species (Table 5).[103, 104] Additionally, increased levels of certain immunoglobulins (antibodies) might be associated with increased B lymphocytes, which primarily produce antibodies, and increased cytokine production. Therefore, with respect to A-bombing effects on the immune system, changes in T lymphocytes and the activation of related inflammatory responses are considered plausible.

Relationship between hematopoietic and immune systems and diseases related to radiation

Radiation-induced genomic changes occur in the hematopoietic and immune systems, particularly in hematopoietic progenitor cells, which are involved in the continual production of blood cells over long periods. Radiation-induced changes in circulating T lymphocytes and markers of inflammation are similar to changes related to aging and those observed at the onset of disease. These findings suggest that radiation exposure induces molecular biological changes in blood cells, which could in part be associated with the risk of certain diseases.

Table 5. Inflammation-related biomarkers in the blood of A-bomb survivors (n=442)

	Increase rate (%)	
	Age (10 years)	Radiation dose (1Gy)
Cytokines		
TNF-α	15	7
INF-γ	4	12
IL-10	8	6
IL-6	24	13
Inflammatory markers		
CRP	25	39
ESR	15	17
Immunoglobulins		
IgA	5	8
IgM	−6	9

Based on the data from Nakachi, *Cancer Sci* 2004

Further detailed investigation of these associations using mouse models and preserved samples from A-bomb survivors might provide insight into the pathogenic mechanisms of radiation-related diseases. For that purpose, RERF research plans to investigate 1) changes similar to aging of T lymphocytes, 2) persistent inflammation, 3) genomic changes in hematopoietic progenitor cells (chromosomal aberrations and somatic mutations), 4) clonal hematopoiesis, and 5) the association between radiation-induced changes at the molecular-biological level in blood cells, taking into account genetic background, lifestyle, cancer, cardiovascular disease, and liver disease (Figure 16).

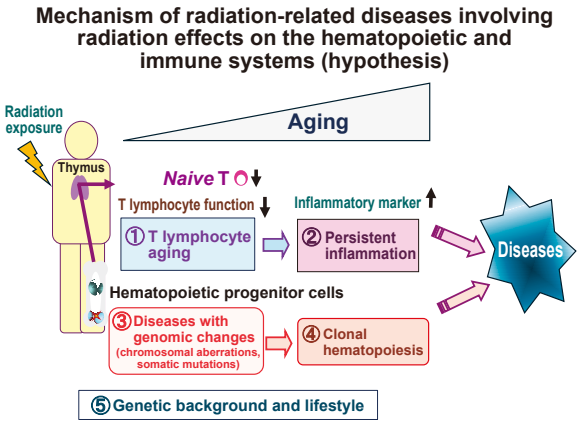


Figure 16. Relationship between the hematopoietic and immune systems and diseases

Radiation-related cancers

Cancer tissue specimens

The Life Span Study (LSS) has shown that the risk of radiation-induced cancer varies by organ, sex, and age at exposure. These differences might be associated with DNA changes in radiation-exposed cells and their ability to proliferate. DNA changes in specific cancer-related genes have been investigated using pathological specimens collected soon after radiation exposure in the LSS. Most pathology specimens preserved at RERF are derived from autopsies and have been degraded and chemically modified by molecule-disruptive (unbuffered) formalin used prior to the 1980s and have also deteriorated over time. As a result, DNA, RNA, and proteins that can be extracted from these specimens are often of insufficient quality for analysis, making molecular-biological analysis extremely challenging. RERF has analyzed the base sequences from extracted DNA and RNA of cancer cells from such deteriorated specimens (Figure 17).

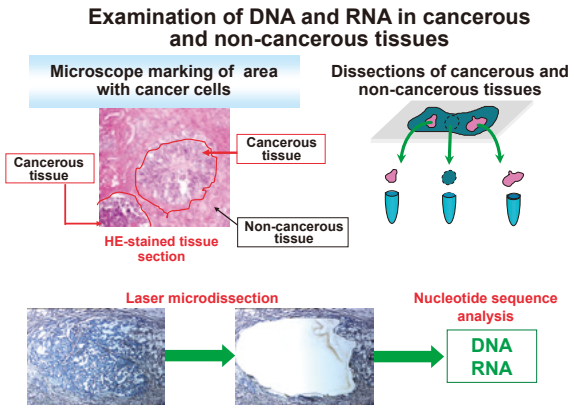


Figure 17. Molecular-biological analysis of cancer tissue specimens

In the 1980s and 1990s, progress was made in identifying cancer-related genes with the development of a technology known as polymerase chain reaction (PCR) used to amplify DNA and RNA. These advances allow detailed investigation of changes in cancer-related genes occurring in human cancer tissues.

Liver and skin cancers

RERF investigated gene mutations in liver cancer[105] and skin cancer[106] among A-bomb survivors, targeting the *p53* tumor suppressor gene and the *PTCH1* oncogene. DNA extracted from autopsy specimens was analyzed using PCR. Radiation exposure was associated with increased frequency of point mutations in the *p53* tumor suppressor gene in hepatocellular carcinoma (Figure 18) and in the *PTCH1* oncogenes in basal cell carcinoma of the skin among A-bomb survivors.

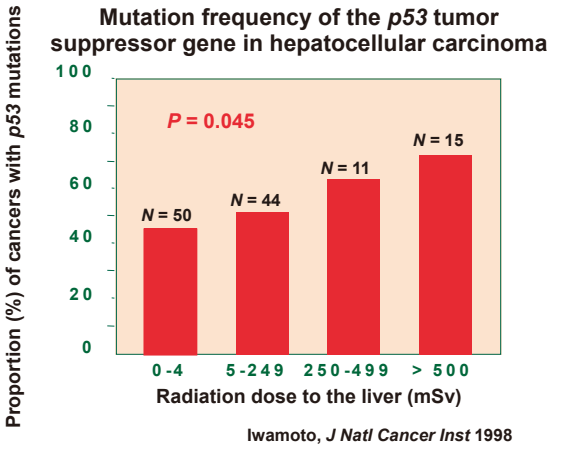


Figure 18. Genetic mutations in liver cancer among A-bomb survivors

Thyroid cancer

RET fusion genes, created by the fusion of the *RET* oncogene to other genes via chromosomal translocation, were detected at high frequency in thyroid cancers of Chernobyl survivors, suggesting that oncogene fusions may be characteristic of thyroid cancer induced by radiation exposure. Compared with other solid cancers, many preserved specimens of thyroid cancer are available from patients who were exposed to the atomic bomb at a young age, who were diagnosed in the early period after exposure, and who had undergone surgical removal of the thyroid.

These specimens have deteriorated, as they were collected long before the Chernobyl accident. Cancerous and non-cancerous parts were carefully separated, and RNA was extracted. Short base sequences from the gene fusion sites were amplified to detect *RET* fusion genes (Figure 19).[107]

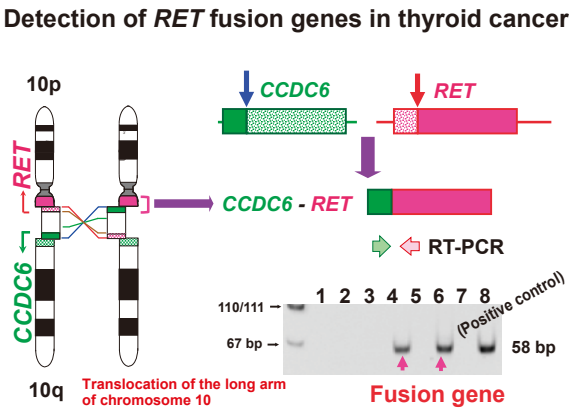


Figure 19. Analysis of fusion genes in thyroid cancer

RERF also worked on detecting fusion genes other than *RET* and were the first in the world to detect *ALK* fusion genes in thyroid cancer.[108] The relative frequency of these fusion genes was higher than that of point mutations, such as *BRAF*,[109] in thyroid cancers of A-bomb survivors exposed to high radiation doses (Figure 20).[108] In addition, the relative frequency of the fusion genes was higher in thyroid cancers that developed earlier after exposure in survivors who were younger at exposure, which was characteristic in young A-bomb survivors, whose thyroid cancer has a shorter latency period. Stable chromosome aberrations occur at a high frequency, depending on the radiation dose. Accordingly, chromosomal translocations at an oncogene locus occur, resulting in fusion gene formation with a high probability.

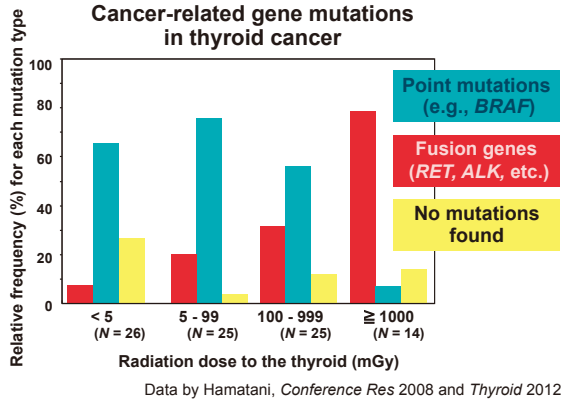


Figure 20. Increased relative frequency of fusion genes in thyroid cancer among A-bomb survivors

The underlying mechanism of radiation-induced thyroid cancer may be explained by thyroid cells acquiring radiation-induced fusion genes and subsequently developing into cancer cells in a growth-phase environment.

Omics analysis

Analysis of limited DNA mutations, such as fusion genes in thyroid cancer, provides only partial understanding of the underlying mechanisms of radiation carcinogenesis. Despite the challenges of conducting genomic analysis using cancer tissue specimens from A-bomb survivors that could deteriorate over time, there is a need to analyze changes in DNA, such as large deletions and methylation in the nucleotide sequences, over a wider range of the genome. RERF has introduced omics-based research, including analysis of tumor cell proteins, to identify new biomarkers of radiation-induced cancers (Figure 21).

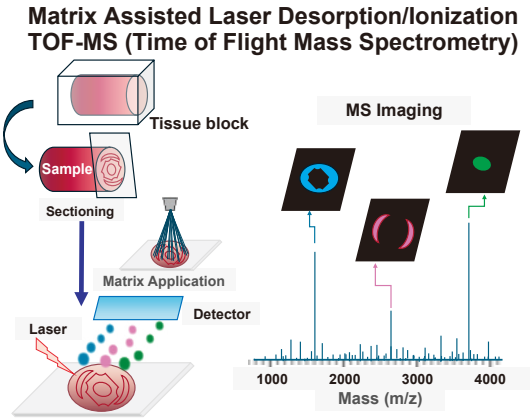


Figure 21. Analysis of cancer tissues using mass spectrometry (MS)

F. Important Research Resources

Biosample Research Center

RERF and ABCC have been conducting health examinations of atomic bomb (A-bomb) survivors and their children for many years. For research purposes, from participants in the Adult Health Study (AHS) including A-bomb survivors, RERF has been provided with and have preserved serum samples since 1969, plasma and blood cells since 1990, urine samples since 1999, and blood clots since 2003, with the informed consent of study participants. RERF has also preserved serum, blood clots, plasma, blood cells, and urine samples provided by participants in the F_1 Offspring Clinical Study, with their consent, during health examinations conducted every four years since 2002. Furthermore, to investigate the transgenerational effects of parental radiation exposure on children at the genetic level (Trio Genome Study), we have preserved blood samples provided by approximately 4,100 individuals, including approximately 1,000 trio families consisting of AHS subjects, their spouses, and their children (subjects of the F_1 Study), since 1985.

For many years, the Departments of Clinical Studies and Molecular Biosciences were responsible for collecting and preserving these samples. In April 2013, RERF established the Biosample Center (renamed the Biosample Research Center in 2019). The purpose was to centrally manage the vast number of samples collected and preserved up to that time and to preserve and manage newly collected samples. In addition, the Center aims to control the quality of the samples and to consolidate a database for comprehensive management of the samples, thereby facilitating the provision of samples to researchers and enabling response to requests from external researchers for use in collaborative studies.

Soon after its establishment, the Center developed standard operating procedures for separating and cryopreserving serum, plasma, blood cell components (mononuclear cells, granulocytes, and erythrocytes), and blood clots from blood samples provided by health examination participants and for cryopreserving urine samples. Starting in 2015, the Center has taken over the preservation of newly provided blood and urine samples from the Departments of Clinical Studies and Molecular Biosciences. Since then, by the end of November 2024, the total number of newly preserved samples at the Center had reached 780,000, including 610,000 blood samples and 160,000 urine samples. Last year (in 2024), the Center newly preserved approximately 61,000 blood samples and 24,000 urine samples provided by approximately 800 AHS participants and approximately 2,300 participants in the F_1 Offspring Clinical Study.

Meanwhile, a total of 1.47 million samples provided by health examination participants before 2015 had been preserved at the Departments of Clinical Studies and Molecular Biosciences. After each sample was cross-checked against the sample inventory with the cooperation of both departments, they were transferred to the Center. Later, in 2021, approximately 60,000 blood cell samples preserved at the Department of Molecular Biosciences for the Trio Genome Study were also transferred to the Center after cross-checking. All together, the number of samples preserved at the Center has reached 2.31 million as of the end of November 2024. Approximately two-thirds, or 1.49 million samples, are stored at the Hiroshima Laboratory, while approximately one-third, or 0.82 million samples, are stored at the Nagasaki Laboratory. Of these samples, 1.37 million were provided by approximately 16,800 AHS participants over a period of more than 50 years since 1969, during approximately 150,000 health examinations. A total of 880,000 samples have been provided by approximately 12,600 participants in the F_1 Offspring Clinical Study, across approximately 45,000 health examinations conducted over more than 20 years since 2002.

Under the current standard operating procedures, AHS participants are asked to provide 9 mL of blood, which is divided into a maximum of 28 tubes for cryopreservation.

Participants in the F_1 Offspring Clinical Study are asked to provide 6 mL of blood, which is divided into a maximum of 18 tubes for cryopreservation. Participants in both studies are asked to provide 4 mL of urine, which is then aliquoted into 8 tubes for cryopreservation. At this time, approximately half of the serum and plasma samples are transported between Hiroshima and Nagasaki for duplicate preservation. Overall, 32% of the preserved blood samples collected during health examinations of the AHS and the F_1 Offspring Clinical Study have been stored in duplicate.

Eighty-seven percent of the preserved samples (2.01 million tubes) are maintained at -80°C. These samples are either stored in a computer-controlled robotic biorepository system (total length: 15 m; see photo), installed at the Hiroshima Laboratory in 2015, or in 45 conventional deep freezers (21 in Hiroshima and 24 in Nagasaki). Additionally, 12% of the samples (270,000 tubes) are stored in 28 liquid nitrogen tanks (21 in Hiroshima and 7 in Nagasaki) at lower temperatures of -150°C to -196°C. These are peripheral blood mononuclear cells (e.g., lymphocytes, monocytes) cryopreserved in a living state. The internal temperatures of the freezers and tanks are continuously monitored, and staff are immediately notified by phone or email if any abnormality occurs.

In 2020, we implemented the Laboratory Information Management System (LIMS) software. This system creates and updates a comprehensive sample database by managing and recording various work processes and information on samples, reagents, and consumables. The process of managing and recording includes sample receipt, component separation, freezing and preservation, quality evaluation, transportation between Hiroshima and Nagasaki, provision to researchers, use, and disposal. Sample information to be managed includes sample inventory, quality, and provision history. In 2021, RERF established a variety of rules and application forms for the research use of samples.

Biosamples stored at the Center have been collected and preserved over many years, along with comprehensive health examination data and epidemiological information. Therefore, analyzing the cells and molecules within these samples is expected to lead to advances such as elucidating the medical effects of radiation at the molecular level; uncovering the mechanisms of radiation-associated cancers and other diseases; and developing biomarkers capable of predicting disease risk. Specifically, this includes the identification of somatic mutations and transgenerational effects caused by radiation exposure through genomic DNA sequencing, as well as the genetic factors contributing to disease. Furthermore, the identification of RNAs, proteins, and metabolites that undergo quantitative or qualitative changes in relation to radiation exposure or disease onset is also anticipated. These findings are expected to contribute to the early detection, prevention, and treatment of various diseases in atomic bomb survivors, their offspring, and the general population.

To make effective use of these preserved samples in the future, it will be necessary to build an integrated research database that links the sample database created by LIMS with clinical and epidemiological data. This integration will allow researchers to quickly and efficiently search for and retrieve samples available for their studies. The transfer of the pathological tissue specimens managed by the Department of Epidemiology and other samples to the Center is also planned. Furthermore, the Center is engaged in research and development of methods for quality evaluation and control of blood samples, as well as in the establishment of standard operating procedures using instruments such as mass spectrometers and cell sorters. Moving forward, we will continue to pursue the development of analytical technologies that apply the latest advancements.

Robotic biorepository system at the Hiroshima Laboratory

Progress of Research and Computing Resources from the Perspective of Information Technology

The Radiation Effects Research Foundation (RERF) was established in 1975, succeeding the Atomic Bomb Casualty Commission (ABCC), which was established in 1947. First, we will trace the historical background from an information technology perspective of the research resources that RERF has collected and managed since the days of ABCC and the computing resources required to utilize these resources. The IBM 1401, a data processing mainframe released by IBM in 1959, is known as the world's first mass-produced general-purpose computer system. ABCC was among the first to adopt it in 1962. Earlier computer systems required a combination of various machines, including a punch machine and a hole inspector for data input, as well as a collator, a sorter, and a tabulator for data collection and processing. Therefore, large-scale work, such as replacing the physical wiring, was required when changing the computational processing according to the research purposes. The general-purpose computer system IBM 1401 was a groundbreaking system that allowed users to input programs and flexibly control processing procedures according to their research parameters. This architecture has been passed down to this day as a fundamental concept that remains relevant today.

Mainframe

Following the establishment of RERF in April 1975, plans were started to introduce a new computer system, and the ACOS System 400, domestically developed and produced by NEC Corporation, was adopted. The operating system supported multiplexing, allowing multiple users to share computing resources at the same time. However, since mainframes at that time had a main memory capacity of only 256 KB, only two or three people were able to use them at the same time. There were many problems with the job dispatching process, and multiplexing was not put into practical use until the mid-1980s. The main memory capacity was later expanded to 48 MB, resulting in a total of more than 200 terminals being connected in Hiroshima and Nagasaki.

This mainframe used its own operating system and was controlled via a command-line interface, where special commands were entered sequentially, word by word. In addition, the programs were coded using FORTRAN or COBOL, and a special control language had to be used to allocate the computing and research resources they required. Therefore, computing was handled exclusively by the Statistical Analysis Room of the Department of Epidemiology and Statistics, which functioned as the information processing division. At that time, a statistician or epidemiologist would review data processing procedures outlined in study protocols prepared by researchers. The Department of Data Processing conducted the data processing, and then an analyst handled the calculation results. For example, calculations using the DS86 radiation dosimetry system, published in 1986, were performed on this mainframe. With the computing resources available at the time, completion of all dose calculations took several months.

Distributed systems

In the 1990s, there was a shift from a system in which multiple users shared a single large computer to a distributed processing system. This system involves distributing and installing different research resources on multiple workstations and accessing each resource via a network. From this time onwards, priority was given to compiling databases of electronic research resources, and databases were distributed across different workstations, i.e., different computing resources, depending on their intended use. As the database construction progressed, the number of installed workstations gradually increased. By 2005, more than 70 workstations had been introduced, with more than 300 terminal devices interconnected.

Computer networks

During the mainframe era, along with the evolution of computing resources, the computer

networks also underwent significant changes. In the mainframe era, networks were dedicated systems for connecting large computers and terminal devices. With the dawn of the Internet in the 1990s and the increasing need for connections to wide area networks, such as the Internet, e-mail, and the World Wide Web, a network system covering the entire facility was introduced. Each unit within the facility is connected via optical fiber cables, and wired network connectors have been installed in the rooms to connect personal computers used as terminal devices. External connection lines for connecting to the Internet have been upgraded to broadband, from 64 kbps → 128 kbps → 256 kbps → 1 Mbps → 100 Mbps. The dedicated line connecting Nagasaki and Hiroshima has also been upgraded to broadband, from a dual line of 128 kbps+256 kbps to ATM (asynchronous transfer mode) at 2 Mbps and then to wide-area Ethernet at 200 Mbps. Meanwhile, the in-house communication bandwidth has evolved from 10Base-T (10 Mbps) to 100Base-TX and further to 1000Base-SX. The current laboratories have upgraded both external connection lines and the dedicated line between Hiroshima and Nagasaki to 10 Gbps.

Future perspectives

Now, celebrating its 50th anniversary, RERF is preparing for a major project of relocation of the Hiroshima Laboratory in FY2026. RERF's strategic plan, formulated in 2022, outlines its commitment to centralizing its unique research resources accumulated over its long history of more than 70 years of mission-driven research. Additionally, RERF will leverage the latest advancements in information science to elucidate the biological mechanisms underlying the effects of radiation on health, cells, and biomolecules. To achieve these ambitious targets, it is undoubtedly important to properly prepare and improve research and computing resources from an information science perspective. Since its inception, RERF has always incorporated cutting-edge information technologies and utilized them effectively to carry out its research mission. We will continue its efforts to build up modern computing and research resources that will befit our status as a world-leading research institution.

G. Activities to Support Research

Joint research with external organizations

The Radiation Effects Research Foundation (RERF) conducts joint research with external organizations in and outside Japan to expand the scope of its research and verify the results of its atomic bomb survivor studies.

One representative example of RERF's international joint research is a long-standing epidemiological study on radiation effects conducted in collaboration with the U.S. National Cancer Institute (NCI). RERF is also engaged in a long-term project in partnership with the German Federal Office for Radiation Protection on mathematical modeling designed to elucidate the mechanisms of cancer development. RERF has also conducted a large-scale, joint study on radiation and immunity funded by the National Institute of Allergy and Infectious Diseases (NIAID) in the United States.

A variety of papers have been published within the framework of a partnership program that RERF has launched with the University of Washington in the United States and Kurume University in Japan for the purpose of epidemiological and statistical studies on A-bomb radiation effects. RERF has also established partnerships with Hiroshima and Nagasaki Universities, enabling researchers to interact beyond institutional barriers and provide lectures for graduate students, thereby contributing to the training of young researchers. Moreover, as a member of the Council of Radiation Effect Research Organizations, RERF engages in information exchange and other forms of interaction with the other members, thereby promoting research, education, and human resource development.

Follow-up studies of A-bomb survivors are useful not only for research on radiation exposure but also to identify cancer-related factors other than radiation. For this reason, RERF has participated in a study led by the National Cancer Center Japan with the aim of proposing cancer prevention measures specifically for the Japanese people, as well as in multiple, large-scale international cohort studies.

The information obtained from health examinations conducted as part of RERF's Adult Health Study, thanks to the cooperation of atomic bomb survivors over the many years, is a valuable resource and asset that can contribute to improvements in health for all people, not just A-bomb survivors. RERF has conducted joint research with Japanese and international partners using this information set, producing results of great value. At present, RERF is participating in a Japanese cohort multi-center joint project that aims to integrate multiple cohort studies in Japan and provide evidence-based information for lifestyle-disease management.

In the area of thyroid research, RERF is participating in a joint research project called the Thyroid Studies Collaboration, which gathers together more than 20 cohorts from around the world and studies risks associated with abnormal thyroid function from a variety of perspectives.

With regard to transgenerational effects of radiation, RERF is planning to conduct genomic DNA research using blood cells from A-bomb survivors and their children, in partnership with RIKEN, the U.S. NCI, Hiroshima University Hospital, and Nagasaki University Hospital. To address the ethical, legal, and social issues (ELSI) in genomic research, RERF is working with Osaka University, the University of Tokyo, the U.S. National Institutes of Health (NIH), and Tohoku University.

Moreover, RERF has also conducted joint research with Kanazawa Medical University, the National Institute of Occupational Safety and Health (Japan), the University of Oxford (U.K.), the University of Rochester (U.S.), the University of Hong Kong (China), the National Institute on Aging (U.S.), and the Helmholtz Institute (Germany), and other national and international institutions, resulting in the publication of numerous papers.

Cancer registry and pathological tissue registry

A cancer registry is a system for the collection of information on cancer incidence (morbidity) and death (mortality) of people diagnosed with and treated for cancer in a specific geographic region to accurately grasp the actual status of cancer patients and propose and assess policies considered necessary to combat cancer. With the large numbers of leukemia cases among A-bomb survivors reported relatively soon after the atomic bombings, local medical associations, the Atomic Bomb Casualty Commission (ABCC), and the Japan National Institute of Health (present-day National Institute of Infectious Diseases) worked together and initiated the Hiroshima City Medical Association Tumor Statistics Project in Hiroshima City in 1957 and the Nagasaki City Tumor Statistics Project in Nagasaki City in 1958. Later, cancer registries were launched in Nagasaki Prefecture in 1985 and in Hiroshima Prefecture in 2002, setting in motion cancer data collection covering the entirety of the prefectures. In 2005, the Hiroshima City Medical Association Tumor Statistics Project was taken over by the City of Hiroshima and reorganized into the Hiroshima City Cancer Registry Project, whereas the Nagasaki City Tumor Statistics Project was integrated into Nagasaki Prefecture's cancer registry program in 2008. With the Cancer Registration Promotion Act coming into effect in 2016 and the subsequent launch of the National Cancer Registry, all cancer patients who had been diagnosed and treated at hospitals in Hiroshima and Nagasaki Prefectures were also registered under this national system.

To date, ABCC/RERF has been commissioned to perform work involving the collection, registration, and management of cancer-related information for the cancer registry programs implemented in Hiroshima and Nagasaki.

In addition to cancer registries, Tumor Tissue Registries were launched in Hiroshima in 1973 and in Nagasaki in 1974, with pathologists affiliated with the prefectural medical associations taking the lead. These so-called Pathological Tissue Registries collect pathological information on benign and malignant tumor diagnoses. Moreover, histopathological specimens of malignant tumors are collected in Hiroshima and Nagasaki, as well as histopathological specimens of benign tumors (excluding adenoid tumors in the stomach and the small and large intestines) in Nagasaki. The Pathological Tissue Registries are carried out only in Hiroshima and Nagasaki in Japan, and RERF has been entrusted with all related work, such as registration and tabulation. In 2005, the Hiroshima Pathological Tissue Registry was integrated into Hiroshima Prefecture's cancer registry, contributing to an upgrade in the precision of diagnostic information of the latter registry. In Hiroshima, that tumor information was collected for the last time with the diagnosis in 2020. In Nagasaki, operation of the Pathological Tissue Registry was transferred from the Nagasaki City Medical Association to the Nagasaki Prefectural Medical Association via the Nagasaki Prefecture Medical Health Operating Group. In Nagasaki, as in Hiroshima, the Pathological Tissue Registry greatly contributed to enhancing the accuracy of the population-based cancer registry, but tumor information provision to the cancer registry was terminated at the end of 2015, following the launch of the National Cancer Registry program. The registries continue to be in operation to date.

The Hiroshima and Nagasaki cancer registries boast a particularly high level of precision by global standards. They are used not only to help implement cancer control measures in those regions but also in international comparisons in studies of cancer incidence and survival, such as the "CI5" (Cancer Incidence in Five Continents) by the International Agency for Research on Cancer (IARC), the International Association of Cancer Registries (IACR), and the CONCORD study of the London School of Hygiene and Tropical Medicine.

Among health effects of atomic bomb radiation, interest is particularly high in cancer incidence. With approval from the entities responsible for the implementation of national or poplation based cancer registries, RERF obtains information about its study participants, conducts epidemiological analysis, and reports results pertaining to the impact of radiation on cancer incidence (for major research results, please refer to "Achievements of major programs over the course of 50 years").

Institutional Review Board

In research involving human subjects, the institutional review board scrutinizes research protocols independently of the researchers from the perspective of the research subjects. In general, its role is to protect the research subjects' right to self-determination, physical and mental safety, and privacy, and to avoid risks and burdens, while ensuring the transparency of the research and gaining the trust of society and the research subjects. The Institutional Review Board of RERF complies with the laws and guidelines of both Japan and the United States for the protection of research subjects, neutrally and fairly reviews research protocols involving human subjects from ethical and scientific standpoints, and issues its opinion on whether or not to approve the research. In accordance with the provisions of laws and guidelines, the committee must be composed of at least five members, including the chair, and must include experts in natural sciences such as medicine and healthcare, experts in the humanities and social sciences such as ethics and law, people who can express opinions from a general perspective, including the perspective of research subjects, and several people who are not affiliated with RERF, and must be composed of both men and women. Currently, the committee consists of a total of 13 members (two co-chairs, seven internal members, and four external members), and three executive secretaries are responsible for the committee's practical operations. The minutes of the committee meetings are available on the websites of RERF and the Ministry of Health, Labour and Welfare.

Compliance with the laws and guidelines of both Japan and the United States is a major feature of ethical review at RERF. U.S. federal regulations for the protection of research subjects apply to research involving human subjects conducted under support of U.S. government agencies, even if it is conducted outside the United States, such as at RERF. Funding for RERF from the U.S. government (primarily the Department of Energy) continues contingent upon RERF's commitment to comply with the laws and guidelines of both Japan and the United States regarding the protection of research subjects. To confirm compliance, the Department of Energy has conducted on-site surveys since 2009, a total of three times (also in 2014 and 2024).

Historically, the system for protecting research subjects of the United States was established through the National Research Act of 1974 and the "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (commonly known as the Belmont Report) of 1979. The National Research Act requires the establishment of ethics committees, and the Belmont Report set out three guidelines: informed consent, risk-benefit assessment, and fair subject selection. Following the establishment of the system for protecting research subjects in the United States, the National Academy of Sciences (NAS) requested that RERF establish a committee to review the ethical aspects of research studies from the perspective of protecting human rights. Therefore, the Human Investigation Committee was established in RERF in 1976. This is believed to be the oldest institutional review board in Japan. In 2001, the Japanese government established the "Ethical Guidelines for Human Genome/Gene Analysis Research," and in the same year, RERF established the "Ethics Committee for Genome Research." The role of this committee was to review genetic analysis research involving human subjects from ethical, legal, social, and scientific perspectives, in addition to the review by the Human Investigation Committee. In 2016, the Human Investigation Committee and the Ethics Committee for Genome Research were merged to form the Institutional Review Board, which continues to this day.

II Contribution to the World and Society

Contribution to the Establishment of Radiation Protection Standards

ABCC/RERF has conducted research on long-term health effects of A-bomb radiation, producing findings that have greatly contributed to the assessment of health risks from radiation carried out by international organizations. In particular, the ABCC/RERF findings have played a key role as a source of information for the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) program involving assessment of the latest findings about radiation health risks. The radiation health-risk information provided by ABCC/RERF is considered to be the most reliable and comprehensive available globally in this field, based on the organization's highly precise radiation dosimetry and long-term morbidity and mortality tracking.

UNSCEAR risk assessment work constitutes the scientific basis for recommendations made by the International Commission on Radiological Protection (ICRP) concerning radiation protection standards for radiation workers and the general public, standards set by the International Atomic Energy Agency (IAEA) and other international organizations, as well as laws and regulations established in countries around the world.

ABCC/RERF research findings also play an important role in the Committee on Biological Effects of Ionizing Radiation (BEIR) of the National Research Council (NRC) of the United States.

Contributions to UNSCEAR risk assessment

Since its establishment in December 1955, UNSCEAR has closely examined data on radiation health risks collected from around the world, scientifically assessed the results of such studies, and published comprehensive reports. Its 1958 report already included a summary of leukemia risk in Hiroshima and Nagasaki.

The results of RERF's radiation effects studies involving atomic bomb survivors played a key role in the UNSCEAR 2006 Report's "Epidemiological studies of radiation and cancer" and "Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure" of Volume I and "Effects of ionizing radiation on the immune system" of Volume II. In Volume II of the 2013 Report, findings from RERF's Life Span Study (LSS) and Adult Health Study (AHS) were prominently featured in a section on the effects of radiation exposure in children.

Contributions to ICRP

The ICRP is an international organization that was established in 1928 to provide expert recommendations on radiation protection. Its recommendations have international authority and constitute the basis for the IAEA's safety standards, as well as laws, regulations, and guidelines for radiological protection in countries around the world.

In its 1990 Recommendations, the ICRP reduced the annual dose limit for radiation workers to an average of 20 mSv per year over a five-year period, based on risk estimates calculated on the basis of RERF's LSS data. The results of RERF's LSS cancer incidence study (1958–1998) also played a key role in the organization's 2007 Recommendations.

As indicated above, ABCC/RERF research findings accumulated over a long period of time have served as a pivotal source of information in UNSCEAR reports and ICRP recommendations, contributing not only to the health and welfare of survivors and their families, but also to the protection of radiation-exposed populations worldwide.

2 Health Checkups for Overseas A-Bomb Survivors

The support program for atomic bomb survivors residing outside Japan was jointly initiated in response to a strong request from survivors living in North America. The main purpose of the program is to alleviate concerns and maintain and enhance health through health examinations and consultations. RERF's physicians and staff continue to participate in the program.

Health consultations for atomic bomb survivors in North America

The health examination program began in North America in 1977 with the dispatch of a medical team jointly organized by RERF and the Hiroshima Prefectural Medical Association. The launch of this program was greatly facilitated by a one-year, fact-finding survey of atomic bomb survivors in the United States conducted by ABCC investigators in 1974.

Prior to implementation, the Hiroshima Prefectural Medication Association had signed a sister-association agreement with each of the local medical associations in the areas where health examinations were scheduled to allow Japanese physicians, who were not licensed to practice medicine in the United States, to conduct health examinations while in the presence of supervising American physicians. To facilitate this approach, the American physicians working at ABCC at the time played a key role.

In this program, the Hiroshima Prefectural Medical Association dispatches a Japanese medical delegation (made up of physicians and administrative staff) mainly to West Coast cities (Los Angeles, San Francisco, and Seattle) and Honolulu in the United States every other year to conduct medical examinations for atomic bomb survivors. Health consultations, also provided in the program, have been a major help to atomic bomb survivors in alleviating their psychological burden and leading a healthier life, given that they are able to discuss their worries and concerns in Japanese and even in the local dialects common in Hiroshima or Nagasaki.

In 2002, the program was redefined as a project commissioned to the Hiroshima Prefectural Medical Association by Hiroshima Prefecture, which is commissioned by the national government, thereby expanding the scope of support as a national project within the framework of the Ministry of Health, Labour and Welfare's support program for overseas atomic bomb survivors. RERF has been charged with the implementation of health examinations and the compilation of reports from the inaugural to the 20th occasions of the event. While the size of the delegation sent overseas has declined in response to the aging of atomic bomb survivors, the program is still in operation, in cooperation with the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE).

Health consultations for atomic bomb survivors in South Korea

Outside Japan, the largest concentration of atomic bomb survivors is found in South Korea. Many were Korean nationals living in Japan at the time of the atomic bombing and later returned to their home country. Since 1991, the Japanese government has contributed funds to the Korean Red Cross for the welfare program providing medical treatment to atomic bomb survivors. In 2004, as part of the national government's support for overseas atomic bomb survivors, a health consultation program for survivors living in South Korea was launched and commissioned to the governments of Nagasaki Prefecture and Nagasaki City. In this program, atomic bomb survivors undergo medical examinations at a hospital affiliated with the Korean Red Cross beforehand, and those results are reviewed and discussed with the examinees through an interpreter. Some survivors still remember

Japanese and speak Hiroshima dialect fluently. The program divides South Korea into six regions, and at the rate of two regions per year, makes a round of the entire country over the course of three years. In 2023, the sixth round began. Since its beginning, physicians at the RERF Nagasaki Laboratory have been participating in the program alongside their colleagues from Nagasaki University and the Japanese Red Cross Nagasaki Genbaku Hospital.

3 Response to Radiation Accidents

Drawing on its expertise, RERF has responded to large-scale radiation accidents by sending medical and technical experts, conducting educational activities on the effects of radiation, participating in studies concerning the effects of the accidents, and serving on committees that examine responses to the affected populations.

1 1986: Chernobyl nuclear power plant accident

- Participation in the International Atomic Energy Agency (IAEA) mission to investigate the health effects of the accident
- Dispatch of doctors for health surveys as part of the Medical Cooperation Project for the Chernobyl Nuclear Power Plant Accident organized by the Sasakawa Health Foundation.

In 1990, doctors were dispatched to the IAEA Chernobyl Accident Health Impact Assessment Mission.

2 1999: Tokaimura JCO criticality accident

- Dispatch of doctors to Tokaimura
- Dispatch of doctors for periodic health examinations of the local residents

放射能の恐怖重く

被爆医療の蓄積生かす

広島から医師団派遣

中国新聞1999年10月2日朝刊34ページ

In 1999, doctors were dispatched for an on-site investigation in Tokaimura (as reported in Chugoku Shimbun on October 2, 1999).

3 2011: TEPCO Fukushima Daiichi Nuclear Power Station accident

- Dispatch of experts in response to a request made to Hiroshima Prefecture by the Ministry of Health, Labour and Welfare and Fukushima Prefecture
- Cooperation in contamination surveys and other initiatives conducted immediately following the accident by the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE)
- Participation in surveys and research concerning and supporting the health of personnel engaged in emergency operations following the Fukushima Daiichi Nuclear Power Station accident

In March 2011, radiation level measurements of soil were conducted in Fukushima Prefecture.

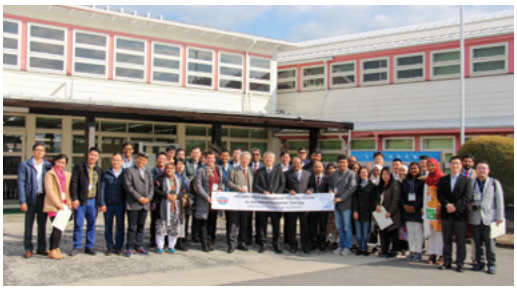
In March 2011, contamination measurements and decontamination advisory activities were conducted in Yamagata Prefecture (at the Governor's Office).

In March 2011, screening tests for evacuated residents were conducted in Fukushima Prefecture.

4 International Collaboration

RERF has been actively engaged in international cooperation to globally disseminate the experience and knowledge that it has gained through its A-bomb survivor research. RERF also accepts many trainees each year through various institutions and organizations.

HICARE



RERF dispatched lecturers and provided the venue for the international training program jointly organized by IAEA and HICARE (2020).

NASHIM

RERF outlined its research to six trainees from South Korea (2023).

Other organizations

RERF accepts visitors and trainees through various organizations, such as the Japan Atomic Energy Agency (JAEA), the Japan International Cooperation Agency (JICA), the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare.

RERF's on-site tour for Australian trainees as part of their training program (2018).

Other activities for international cooperation

- Activities in partnership with the World Health Organization (WHO)
- Activities in partnership with the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)
- Activities in partnership with the International Commission on Radiological Protection (ICRP)
- Others

RERF researchers dispatched as lecturers at the request of Korea University (2024).

At the request of the City of Hiroshima, each year on August 6, RERF welcomes at the Hiroshima Laboratory ambassadors and governmental representatives following their attendance at the Peace Memorial Ceremony in Hiroshima. The guests are provided a lecture and on-site tour to deepen their understanding of the effects of radiation on the human body.

Participation in activities by the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE)

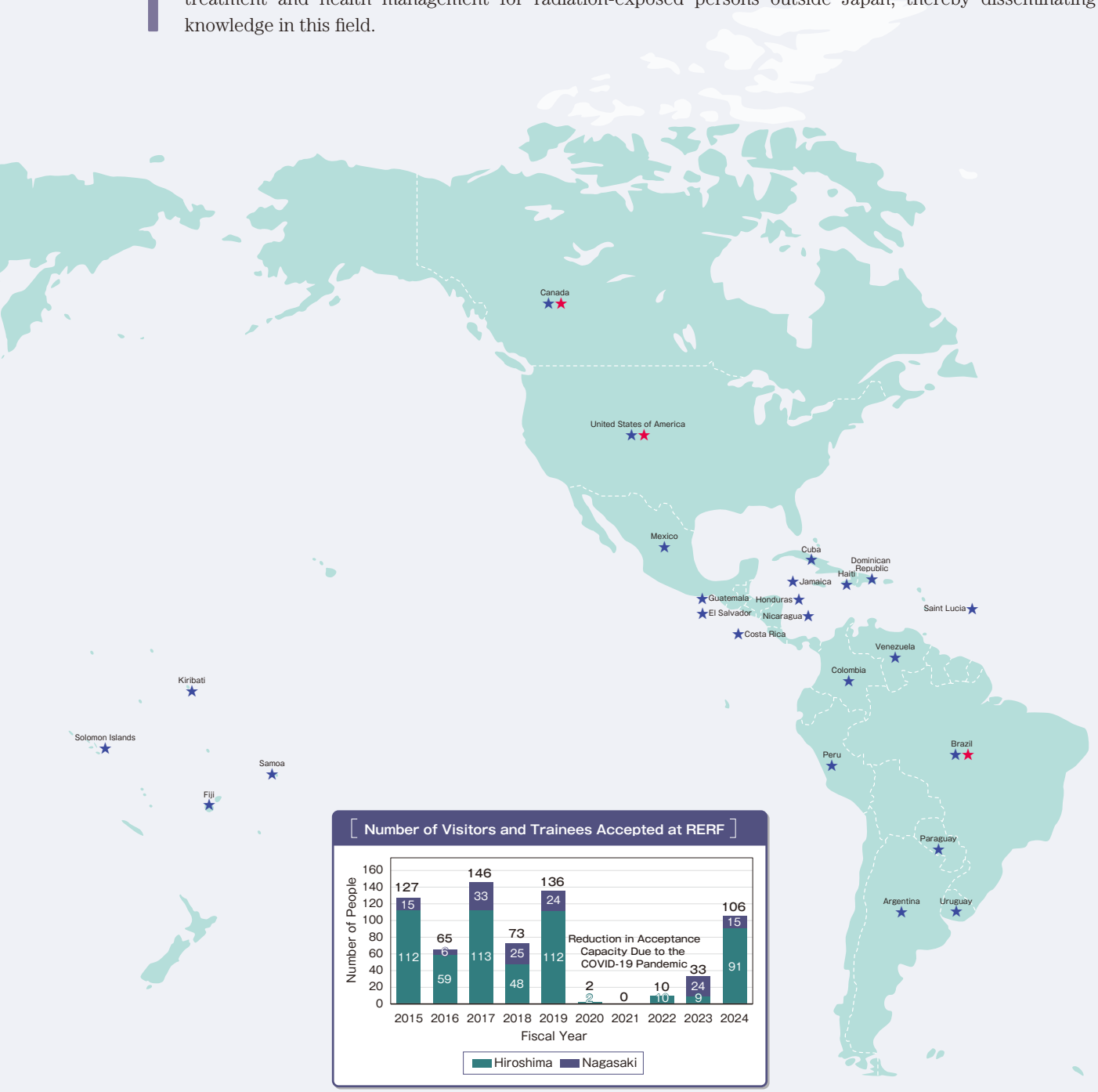
RERF conducts training in Hiroshima for medical professionals from around the world on medical care for radiation-exposed persons and dispatches physicians and specialists internationally to spread knowledge about medical care for radiation-exposed persons.

★ Overseas dispatch of RERF experts

From April 2007 to March 2024, RERF officials and staff were dispatched to 10 countries in total under the "Dispatch of Japanese Experts" program as part of the "International Exchange and Research Project on Health Effects of A-bomb Radiation" commissioned by the Ministry of Health, Labour and Welfare. The 10 countries are marked on this map with ★ under the name of each country.

Participation in activities by the Nagasaki Association for Hibakushas' Medical Care (NASHIM)

RERF participates in training programs for healthcare professionals engaged in medical examinations and treatment and health management for radiation-exposed persons outside Japan, thereby disseminating knowledge in this field.



★ Acceptance of visitors and trainees from abroad

Through the Japan International Cooperation Agency (JICA) and other organizations, RERF accepts visitors and trainees from countries and regions around the world, including Asia, the former Soviet Union, Europe, the United States, South America, the Middle East, Africa, and Oceania. From April 2007 through December 2024, RERF welcomed a total of 1,611 visitors and trainees (1,365 in Hiroshima, 246 in Nagasaki) from over 100 countries (marked with ★).

II About the Organization

Evolution of the Organization

About the Organization

Locations

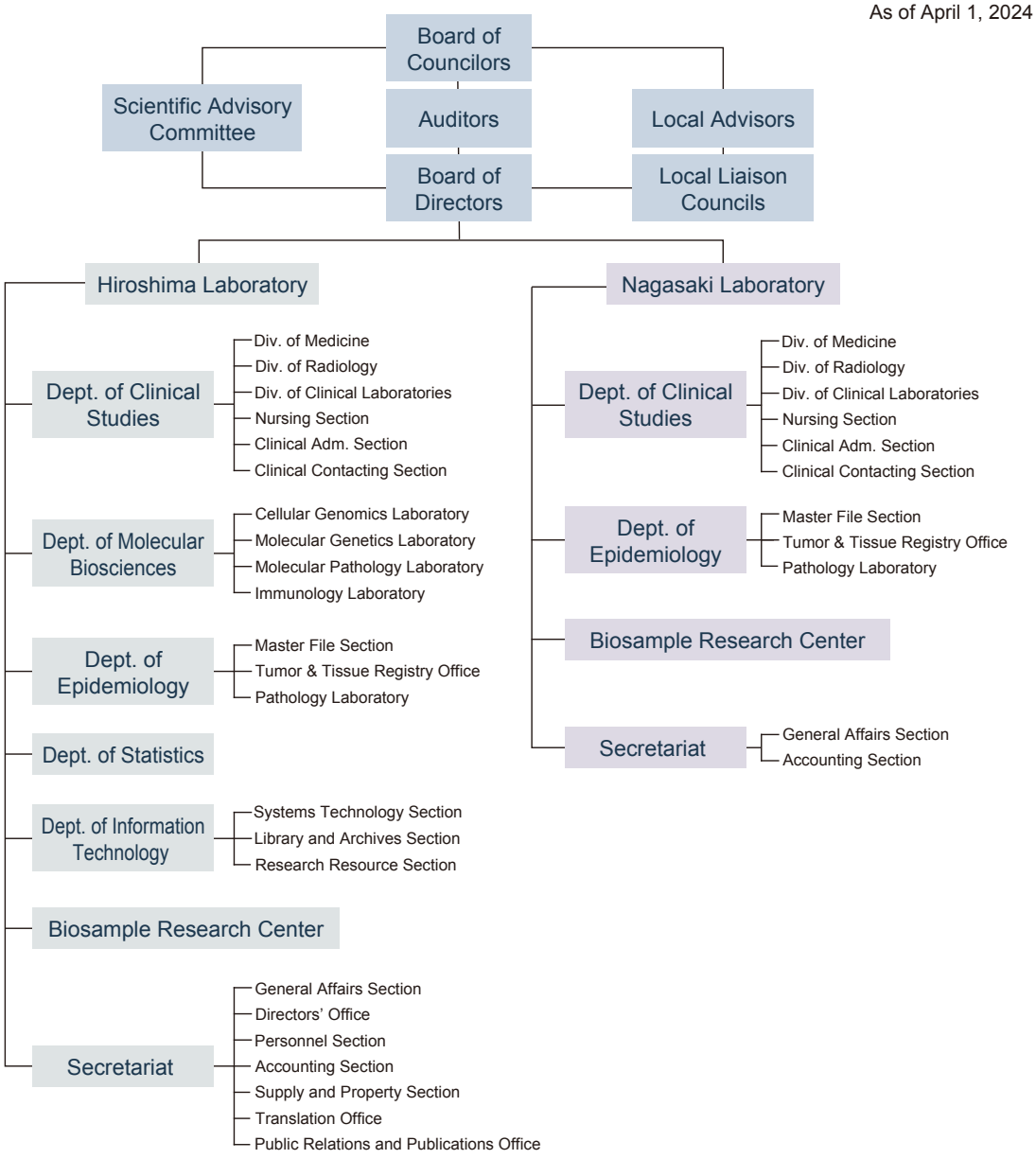
Hiroshima Research Institute
Address: 5-2 Hijiyama Park, Minami-ku, Hiroshima City, Hiroshima Prefecture, 732-0815, Japan
TEL: 082-261-3131

Nagasaki Research Institute
Address: 1-8-6 Nakagawa, Nagasaki City, Nagasaki Prefecture, 850-0013, Japan
TEL: 095-823-1121

Organizational Structure

The highest decision-making body of the organization is the Board of Councilors, composed of members selected from both Japan and the United States. The institute operates its business in accordance with the Articles of Incorporation determined by the Board of Councilors.
The Board of Directors is responsible for the management and operation of the institute's activities.
The Auditors conduct audits on the Directors' duties and the financial status of the institute. Both Directors and Auditors are appointed by the Board of Councilors.

As of April 1, 2024



List of Chairs, Vice-chairs

Chair

Appointed	Resigned	Name
1975/4/1	1978/6/30	Hisao Yamashita
1978/7/1	1981/6/30	Masao Tamaki
1981/7/1	1997/6/30	Itsuzo Shigematsu
1997/7/1	2001/6/30	Shigenobu Nagataki
2001/7/1	2005/6/30	Burton G. Bennett
2005/7/1	2015/6/20	Toshiteru Okubo
2015/6/20	2023/6/22	Ohtsura Niwa
2023/6/22	Present	Kenji Kamiya

Vice-chair

Appointed	Resigned	Name
1975/4/1	1978/6/30	LeRoy R. Allen
1978/7/1	1979/8/7	Stuart C. Finch
1979/9/4	1981/6/30	William J. Schull
1981/7/1	1983/6/30	Anthony V. Pisciotta
1983/7/1	1985/9/30	Abraham Kagan
1985/10/1	1987/8/20	Charles W. Edington
1987/8/21	1993/6/30	J. W. Thiessen
1993/7/1	1995/7/3	Mortimer L. Mendelsohn
1995/9/9	1996/6/27	Seymour Abrahamson
1996/6/27	1997/1/22	William J. Schull
1997/1/22	2000/10/20	Sheldon Wolff
2000/10/20	2001/6/30	Seymour Abrahamson
2001/7/1	2005/3/31	Senjun Taira
2005/4/1	2005/6/30	Toshiteru Okubo
2005/7/1	2005/12/31	Charles A. Waldren
2006/1/1	2015/6/20	Roy E. Shore
2015/6/20	2023/6/22	Robert L. Ullrich
2023/6/22	Present	Preetha Rajaraman

Transition of Organization

April 1, 1975

Hiroshima Laboratory
Dept. of Medicine
Dept. of Radiology
Dept. of Pathology
Dept. of Clinical Laboratories
Dept. of Epidemiology & Statistics
Medical Sociology Department
Secretariat

Nagasaki Branch
Dept. of Medicine
Dept. of Pathology
Dept. of Clinical Laboratories
Medical Sociology Department
Secretariat

July 1, 1981

Hiroshima Laboratory
Dept. of Medicine
Dept. of Radiology
Dept. of Pathology
Dept. of Clinical Laboratories
Dept. of Epidemiology & Statistics
Dept. of Research Support
Secretariat

Nagasaki Branch
Dept. of Medicine
Dept. of Pathology
Dept. of Clinical Laboratories
Secretariat

April 1, 1984

Hiroshima Laboratory
Dept. of Medicine
Dept. of Radiology
Dept. of Pathology
Dept. of Clinical Laboratories
Dept. of Epidemiology & Statistics
Dept. of Research Support
Computer Center
Secretariat

Nagasaki Branch
Dept. of Medicine
Dept. of Radiology
Dept. of Pathology
Dept. of Clinical Laboratories
Dept. of Epidemiology & Statistics
Dept. of Research Support
Secretariat

August 1, 1985

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Computer Center
Dept. of Research Support
Secretariat

Nagasaki Branch
Dept. of Clinical Studies
Dept. of Radiobiology
Dept. of Epidemiology & Biometrics
Dept. of Research Support
Secretariat

August 1, 1987

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Epidemiologic Pathology
Research Information Center
Research Support Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Radiobiology
Dept. of Epidemiology & Biometrics
Dept. of Epidemiologic Pathology
Research Support Center
Secretariat

January 1, 1990

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Epidemiologic Pathology
Research Information Center
Research Support Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Radiobiology
Dept. of Epidemiology & Biometrics
Dept. of Epidemiologic Pathology
Secretariat

May 1, 1991

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Epidemiologic Pathology
Research Information Center
Publication & Document Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Radiobiology
Dept. of Epidemiology & Biometrics
Dept. of Epidemiologic Pathology
Secretariat

July 1, 1995

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Research Information Center
Publication & Document Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Radiobiology
Dept. of Epidemiology
Secretariat

October 1, 1995

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Information Technology
Publication & Document Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Radiobiology
Dept. of Epidemiology
Secretariat

April 1, 1996

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Information Technology
Publication & Document Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Epidemiology
Secretariat

July 1, 2000

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Information Technology
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Epidemiology
Secretariat

July 15, 2002

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology & Molecular Epidemiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Information Technology
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Epidemiology
Secretariat

April 1, 2013

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Genetics
Dept. of Radiobiology & Molecular Epidemiology
Dept. of Epidemiology
Dept. of Statistics
Dept. of Information Technology
Biosample Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Epidemiology
Biosample Center
Secretariat

January 1, 2017

Hiroshima Laboratory
Dept. of Clinical Studies
Dept. of Molecular Biosciences
Dept. of Epidemiology
Dept. of Statistics
Dept. of Information Technology
Biosample Research Center
Secretariat

Nagasaki Laboratory
Dept. of Clinical Studies
Dept. of Epidemiology
Biosample Research Center
Secretariat

2 RERF in the Future

The Radiation Effects Research Foundation (RERF), conducting studies and research on long-term health effects of radiation exposure based on the understanding and dedication of atomic bomb survivors and their children over many years, has recently reached a major milestone — the 50th anniversary of its establishment. RERF's research results, which have contributed to the health management and improvement in health care and welfare of the A-bomb survivors, are highly regarded by international organizations and serve as the foundation for radiation protection systems around the world.

Ahead of its 50th anniversary, RERF designed a strategic plan for its future activities. In doing so, RERF focused primarily on its research resources and the achievements deemed possible in the future through its unique work. RERF's scientific resources, unrivaled by other research institutes in the world, include I) a Life Span Study cohort of approximately 120,000 individuals followed throughout their lives, an in utero exposure study cohort, a study cohort of A-bomb survivors' children, and their respective clinical study populations and databases; and II) a store of more than two million biosamples, which is among the largest grouping of such samples in the world. Among the health issues related to radiation confronting humanity, there are some only RERF is capable of resolving through its work. Such issues include questions about 1) lifetime risk of disease following radiation exposure, 2) radiosensitivity at all ages, especially during the fetal period and early childhood, and 3) comprehensive genetic effects of radiation. These make up the mission that has been entrusted to RERF.

As for future research achievements, remarkable advances in genomics and multi-omics analysis of biomolecules in recent years have made it possible to conduct comprehensive analysis of biomolecules using biosamples, enabling molecular-level elucidation of the mechanisms of radiation effects, work that simply was not possible in the 20th century. Indeed, we are entering a new era in this regard. RERF's research is expected to lead to the identification of biomarkers for cancer and other diseases and the elucidation of disease-onset mechanisms, both based on comprehensive analysis of the biosamples donated on a regular basis, including earlier periods of good health, by RERF study participants. Moreover, whole-genome analysis can be applied to promote research into radiation effects at the genome level, potentially leading to, for example, more scientifically precise clarification of health effects from low-dose radiation exposures.

With that, RERF's strategic plan was designed on the basis of the following four pillars:

1. Continuation and completion of epidemiological studies and research
2. Mechanistic research on radiation effects using biosamples
3. Promotion of collaborative research
4. Contribution to A-bomb survivors and their families, the scientific community, and society

Advanced research at that level will require the development of new facilities. Fortunately, thanks to the dedicated efforts of many parties concerned, RERF's long-awaited relocation has officially been decided, with the construction of a new research building underway on the Kasumi Campus of Hiroshima University. With this as a new beginning, RERF intends to establish itself as an international hub of radiation effects research and will work to enhance health care for A-bomb survivors in partnership with Hiroshima University Hospital, to develop and train appropriate personnel based on utilization

of the educational functionality of Hiroshima and Nagasaki Universities, and to create international networks and platforms for collaborative research with the two universities as well as with other universities and research institutions both in Japan and around the world.

In this milestone year marking the 80th commemoration of the atomic bombings and the 50th anniversary of RERF's establishment, the organization is entering a period of the most dramatic change since it first opened its doors, marked by the adoption of a new future vision and the construction of new research facilities. On this occasion, the directors and staff at RERF are determined to continue working together to help promote RERF's further development, steadfastly taking on the most difficult challenges in the belief that the most effective way to repay the A-bomb survivors and their children and families for their cooperation and trust in RERF is to continue our research into the health effects of A-bomb radiation exposure.

We ask for the continued support and guidance from all parties concerned.

Ⅳ Laboratories

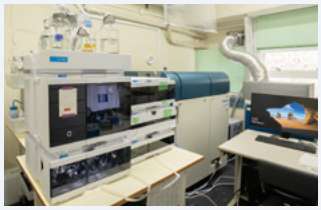
Hiroshima Laboratory

The Hiroshima Atomic Bomb Casualty Commission (ABCC) was established in March 1947 by leasing a part of the Hiroshima Red Cross Hospital. After moving to the former Gaisen-kan Hall in the Ujina district of Hiroshima City in January 1948, ABCC relocated to its current location on Hiroshima's Mt. Hijiyama in November 1950. The historic buildings are characterized by a distinctive arch-shaped structure.

In 2023, the decision was made to relocate the RERF Hiroshima Laboratory to the Kasumi Campus of Hiroshima University (1-2-3 Kasumi, Minami-ku, Hiroshima City).

Hiroshima Laboratory

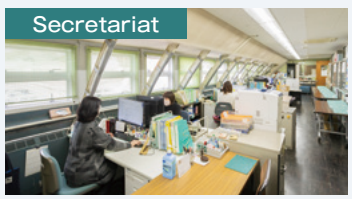
Department of Clinical Studies



Biosample Research Center

Department of Molecular Biosciences

Hijiyama Hall



Secretariat

Department of Statistics

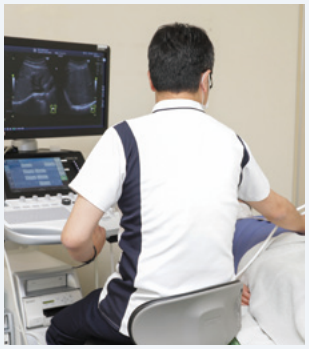
Department of Epidemiology

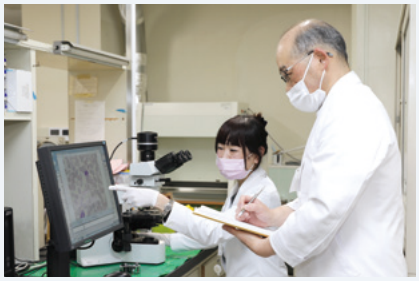
2 Nagasaki Laboratory

Nagasaki Laboratory

The Nagasaki Atomic Bomb Casualty Commission (ABCC) was established in July 1948 in one corner of the Nagasaki Medical College Hospital (former Shinkozen Elementary School). After moving to the Nagasaki Prefectural Education Hall (in the area of Sakurababa-cho, Nagasaki City) in 1949, ABCC relocated to its current location (in Nakagawa, Nagasaki City) in 1982. The RERF Nagasaki Laboratory is conveniently located in front of the streetcar stop "Hotarujaya."

Department of Clinical Studies

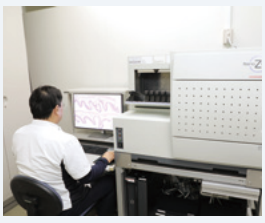




Biosample Research Center

Department of Epidemiology

Secretariat



V Glossary

Glossary

Radioactivation

A phenomenon in which a substance becomes radioactive when exposed to neutrons or high-energy radiation. This process causes a substance that was not originally radioactive to begin emitting radiation.

Physical dose

The gray (Gy) is the unit of absorbed radiation dose (1 Gy = 1,000 mGy). One Gy is equivalent to one joule of absorbed radiation energy per kilogram of matter (J/kg). (The joule is a unit of energy, work, or heat.)

Weighted absorbed organ dose

The dose of radiation energy absorbed by a particular organ or tissue divided by its weight. It is expressed in gray (Gy). Atomic bomb radiation comprised gamma rays and a small fraction of neutron radiation (less than a few percent of the total dose). Neutrons have a more potent effect on living tissue than gamma rays when compared at the same dose. The weighted absorbed dose is defined as the sum of the neutron dose multiplied by a weighting factor (reflecting its greater biological impact) and the gamma-ray dose. RERF currently uses weighted absorbed doses with a weighting factor of 10 to evaluate radiation effects on each organ (the weighted absorbed dose is also referred to as the weighted absorbed organ dose or the absorbed organ dose with weighting factor).

Prevalence and incidence

Prevalence refers to the proportion of patients diagnosed with a disease or medical condition at a given point in time, regardless of when the disease or medical condition first developed. Incidence refers to the rate of patients newly diagnosed during a given time period (typically one year).

Relative risk (RR)

The ratio of the incidence of an event (or mortality) occurring in a population exposed to radiation relative to that in an unexposed population. An RR of 1 implies that it has had no effect on risk.

Excess relative risk (ERR)

The increase in the ratio of the incidence (mortality) occurring among members of a population exposed to radiation as compared to that in an unexposed population. An ERR is calculated as RR–1. An ERR of 0 implies that exposure has had no effect on risk.

Excess absolute rate (EAR) (Note: also expressed as excess absolute risk)

The excess absolute rate (EAR) is calculated by subtracting the incidence (or mortality) in an unexposed population from the incidence (or mortality) in a population exposed to radiation. In other words, the EAR represents the absolute increase in the rate.

Excess number of cases (or deaths)

The additional number of cases (or deaths) due to radiation exposure, calculated by subtracting the number of cases (or deaths) observed in the unexposed group from the number of cases (or deaths) observed in the exposed group within a specified cohort or population.

Attributable fraction (AF)

The increase in the outcome (incidence or mortality) due to radiation exposure in the population under observation. For effect at the population level, AF is referred to as population attributable fraction (PAF).

Confidence interval (CI)

A range that contains the true but unknown value for the entire target group (population) with a specified probability when estimating it (e.g., the mean or radiation effect) based on data sampled from the population. For example, suppose data were collected from 100 individuals to evaluate the therapeutic effect of a particular drug, and the drug was found to reduce body weight by an average of 3 kg. This result is obtained based on samples from the population and may not match the average effect (true effect) in the population. Since data naturally varies, another sample of 100 individuals may show an average weight loss of 4 kg. Then, a range is estimated in which the true effect of the drug would lie and be expressed, for example, as (1 kg, 5 kg). A 95% confidence interval represents an estimated range that is expected to contain the true effect with a probability of 95% if the estimation is repeated using data sampled from the same population. (For example, if you estimated the interval 100 times in this way, about 95 times of that interval would be expected to contain the true effect.) If the excess relative risk (ERR) is greater than 0 and its 95% confidence interval does not include 0, it is interpreted as a "significantly increased risk."

Genome

The entire set of genetic information composed of DNA (deoxyribonucleic acid). Genetic information is contained in the order (sequence) of four types of bases in DNA, called adenine (A), thymine (T), guanine (G), and cytosine (C). The genome contains an enormous number of genes that regulate cellular protein synthesis.

Chromosome

A complex of genomic DNA and proteins in cells. It appears as a rod-shaped structure during cell division. In humans, most nucleated cells, except red blood cells, contain 23 pairs of chromosomes, with one chromosome inherited from the mother and the other from the father (46 chromosomes in total). Chromosomal aberrations occur when two chromosomes, broken by radiation exposure or other reasons, abnormally recombine with each other. There are two types of aberrations based on how the chromosomes are recombined: cells carrying unstable-type aberrations die during division, whereas cells carrying stable-type aberrations can survive after cell division, with the aberrations retained. The latter mutations can be detected long after radiation exposure.

DNA mutations

Changes in the arrangement (sequence) of the four bases (A, T, G, and C), including single nucleotide variants (SNVs), in which one base is replaced by another type of base; insertion/deletion variants (Indels), in which one or more bases are inserted or deleted; multisite variants (MSMs), in which multiple bases are replaced by other types of bases; and structural variants (SVs), in which a large portion of DNA (typically 50 bases or more) is changed (e.g., duplications, insertions, and deletions).

Hematopoietic and immune systems

Leukocytes, which are a type of blood cell, are primarily responsible for the body's immune system and include granulocytes, monocytes, and lymphocytes (T, B, and NK lymphocytes). They originate from hematopoietic stem cells, which also produce erythrocytes and platelets. The bone marrow, which produces hematopoietic stem cells and these blood cells, and the organs and tissues that support the differentiation and maturation of lymphocytes derived from the bone marrow are responsible for immunity (e.g., thymus, spleen, and lymph nodes) and are collectively referred to as the hematopoietic and immune systems.

Biomarker

A diagnostic parameter used to monitor health or predict the presence or progression of disease. These include familiar markers, such as blood pressure and blood test parameters, as well as markers used to evaluate specific functions (e.g., immunity), such as blood cytokine levels. RERF's molecular biology research is exploring biomarkers associated with the risk of radiation exposure-related disease.

Omics

A research methodology that comprehensively investigates a wide variety of biomolecules (e.g., genomic DNA and proteins) to analyze their interactions and functions. Omics analysis may reveal the complete picture of the mechanisms underlying radiation effects, which are only partially understood at present.

Hypocenter

Defined as the point on the ground directly beneath the A-bomb detonation.

VI References

References

Ⅰ Research Activities

2. Major Program Achievements Over 50 Years

A. Studies of A-Bomb Survivors

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