A BRIEF DESCRIPTION

Radiation Effects Research Foundation

A Japan-US Cooperative Research Organization

Inside cover: (left) Radiation Effects Research Foundation in Nagasaki
(right) Radiation Effects Research Foundation in Hijiyama Park, Hiroshima

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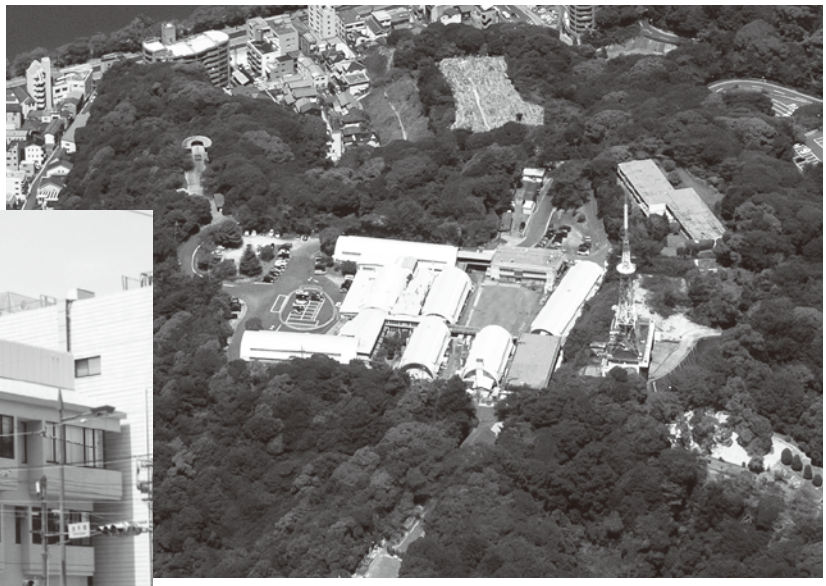

放影研
RERF

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Preface

The Radiation Effects Research Foundation (RERF) was established to "conduct research and studies for peaceful purposes on medical effects of radiation and associated diseases in humans, with a view to contributing to maintenance of the health and welfare of the atomic bomb survivors and to enhancement of the health of all humankind," as stipulated in Article 3 of the RERF Articles of Incorporation. RERF scientists from the United States and Japan conduct multidisciplinary research in numerous fields of science including epidemiology, clinical medicine, genetics, and immunology to elucidate health effects of atomic bomb (A-bomb) radiation in cooperation with A-bomb survivors, as well as Hiroshima and Nagasaki citizens, local medical associations, universities, and governmental agencies, among others. Thanks to the continued understanding and cooperation of A-bomb survivors and numerous others over many years, RERF's research results are widely used to promote the health and welfare of A-bomb survivors, support radiological medical research throughout the world, and contribute to reduction of risk from medical and other types of radiation exposures.

RERF's predecessor organization, the Atomic Bomb Casualty Commission (ABCC), was founded by the U.S. National Academy of Sciences (NAS) in 1947 to conduct research in the city of Hiroshima, with funding provided by the U.S. Atomic Energy Commission. The following year, 1948, ABCC's Nagasaki Laboratory was established. ABCC initiated health studies of A-bomb survivors in cooperation with the Japan Ministry of Health and Welfare's National Institute of Health, which joined the research program in 1948. In 1955, the Francis Committee was convened to conduct a comprehensive review of ABCC work. The Committee recommended that fixed cohorts be established to conduct population-based follow-up studies. This recommendation laid the foundation for the RERF research policies that remain in place today.

RERF was established under Japanese civil law on April 1, 1975, as a nonprofit foundation under the jurisdiction of the Japan Ministry of Foreign Affairs and Ministry of Health and Welfare. RERF is operated binationally, in accordance with an agreement between the governments of Japan and the United States. When ABCC was reorganized to form RERF, RERF assumed ongoing responsibility for ABCC's research activities. Based on RERF's transition to a public interest incorporated foundation on April 1, 2012, the organization was further strengthened with a management structure comprised of the Board of Councilors, Board of Directors, and Auditors. The Scientific Advisory Committee, consisting of both U.S. and Japanese Advisors, makes annual recommendations that form the basis for RERF's research activities. RERF reports on its research activities to the Hiroshima and Nagasaki Local Advisors and Local Liaison Councils and strives to reflect the views and opinions of those individuals and bodies in its work.

The goal of ABCC-RERF research is to elucidate the long-term effects of radiation on human health. RERF research can be characterized as long-term follow-up studies of large well-organized cohorts. RERF's follow-up studies are unique in the world in terms of scale, composition, accuracy, and other important aspects. RERF's health effects studies are notable for maintaining a high participation rate since their initiation. As of 2014, although nearly 70 years have passed since the atomic bombs were dropped on Hiroshima and Nagasaki, up to 30 more years may be necessary to complete the lifetime follow-up of all A-bomb survivors including those who were young at the time of the atomic bombings, meaning that the foundation's research is not yet finished. New findings from RERF studies have been used not only for the medical care and welfare of A-bomb survivors but also for the establishment of international radiation protection standards. For this reason, RERF's research remains the focus of continued attention from international governmental and private organizations and other groups.

RERF has done its best to consistently release accurate information about the aforementioned research results. In addition to scientific presentations and journal publications, we have issued a variety of published materials to outline our activities. As is the case generally for such materials, this "A Brief Description" has undergone several revisions. This time, intending to set the booklet clearly apart, we made extensive revisions with the aim of reaching persons who already possess basic knowledge about radiation as well as those who are experts in the field of radiation. This revised version explains the late effects of A-bomb radiation primarily based on ABCC-RERF reports, under an editorial policy of introducing results obtained thus far as well as expectations for future research.

RERF will continue to make every effort to carry on our mission of conducting long-term follow-up research of A-bomb survivor cohorts and producing further research results. It is our strong desire that scientific clarification of the health effects resulting from A-bomb radiation will lead to the shared conviction among the world's people that the tragedies of Hiroshima and Nagasaki must never be repeated, thereby laying the foundation for lasting peace.

【1】 Physical destruction by the atomic bombs

The atomic bomb dropped on the city of Hiroshima using uranium-235 (^{235}U) as fissile material exploded with an energy equivalent to 16 kilotons of TNT. The atomic bomb dropped on the city of Nagasaki used plutonium-239 (^{239}Pu) as fissile material, releasing energy equivalent to 21 kilotons of TNT. The estimated energy yields of the bombs were comprised of 50% blast (shock wave), 35% heat wave, and 15% radiation.

The atomic bombs fell on Hiroshima at 8:15 a.m. on August 6, 1945, and on Nagasaki at 11:02 a.m. on August 9, 1945. The Hiroshima bomb exploded approximately 600 m above Shima Hospital, about 160 m southeast of the Atomic-bomb Dome (former Hiroshima Prefectural Industrial Promotion Hall); in Nagasaki the bomb exploded 503 m above the vicinity of the Matsuyama-machi intersection in the northern part of the city. At the instant of explosion, the temperature at the center of each bomb reached millions of degrees Celsius and the atmospheric pressure hundreds of thousands of atmospheres. A fireball formed around the exploding A-bomb and within it, a secondary nuclear reaction was underway.

Shock waves generated on the surfaces of the fireballs created by the Hiroshima and Nagasaki A-bombs spread through the atmosphere at supersonic speeds. The shock waves of each bomb were accompanied by a strong blast that inflicted serious damage when it hit the ground. The blast traveled 1 km from the hypocenter in two seconds after the detonation, 2 km in 4.5 seconds, and about 11 km in 30 seconds. The velocity was estimated to be 280 m/second around the hypocenter and 28 m/second at the distance of 3.2 km from the hypocenter. After the blast passed over the vicinity of the hypocenter, the area was subjected to negative pressure from outward wind. Inward wind then blew back through the area, giving rise to a rapid ascending current that formed the stem of a mushroom cloud. The combination of the shock waves and the blast caused catastrophic damage to wooden houses within 2 km of the hypocenter. Even many reinforced concrete buildings located within 0.5 km of the hypocenter collapsed. Due to the shock waves and blast, many people died or were injured after being buried under collapsed buildings or hit by heavy flying objects or broken glass.

The surface temperature of the fireball 0.3 seconds after the explosion was estimated to be approximately 7,000°C, and that of the ground just below the epicenter reached approximately 3,000–4,000°C. Wood surfaces charred by the heat waves (infrared rays) were observed within about 3 km and 3.5 km of the hypocenter in Hiroshima and Nagasaki, respectively. These thermal waves burned any exposed skin of people within 3.5 km and 4 km of the hypocenters in Hiroshima and Nagasaki, respectively. In both cities, people within approximately 1.2 km of the hypocenter and who had no shielding were fatally burned. It is estimated that 20–30% of the human deaths were attributable to burns caused by the thermal waves.

Various forms of ionizing radiation emitted by the nuclear explosion of an atomic bomb, such as neutrons, α particles, β particles, and γ rays (hereinafter known simply as "radiation"), are called primary radiation or prompt radiation. Of these forms of primary radiation, neutrons can render bomb debris and airborne molecules radioactive. This process of activation can generate various types of radioisotopes, giving rise to secondary radiation, also known as delayed radiation. Although this process was completed very rapidly after the explosions, radioisotopes generated in the fireballs continued to emit radiation for more than one minute. During this sequence, most α and β particles disappeared, leaving mostly neutrons and γ rays to reach the ground.

The primary radiation explained above is also called initial radiation or direct radiation. A-bomb radiation is classified into initial radiation and residual radiation.

Residual radiation was caused by secondary radiation resulting from radioactive materials that remained in the environment from the nuclear detonations. This type of radiation can further be classified into induced radiation and fallout radiation, the latter from radioactive substances scattered in the air. Induced radiation was caused by temporary activation of the neutrons in the atoms making up certain substances in the metals of some buildings and in soil. Most of the exposure to induced radiation, excluding exceptional cases of fine particle inhalation, was external, and most of the induced radioactivity decreased rapidly within a few days after the bombings.

On the other hand, the remaining A-bomb source materials and secondary radioactive materials generated by the nuclear detonations rose high in the air with the fireballs and were widely scattered in the

Note) Units of radiation used in this pamphlet: Radiation units are frequently expressed as sievert (Sv), but "A Brief Description" uses gray (Gy). For more detailed information regarding Sv and Gy, refer to the description "Weighted absorbed organ dose" in the Glossary section (on page 47).

atmosphere. A portion of the radioactive particles suspended in the air gradually fell to the ground, with such movement accelerated by rain and other forms of precipitation. So-called “black rain” is thought to have contained radioactive fallout. The cause of the black rain color was actually soot from the secondary fires, and therefore the rain’s color was not directly indicative of the level of radioactivity. The possibility exists that even the rain falling soon after the explosions that was not black might have contained radioactive substances and that some of the rain that was black had essentially no radioactivity.

With regard to these particles, we need to consider both external exposure from radioactive substances that remained in the air or that fell to and accumulated on the ground and internal exposure, which was caused by direct inhalation of particles remaining in the air and by intake of radioactive substances reaching the ground and into the body by way of various pathways. Such internal exposure pathways included direct intake of radioactive fallout on the ground mixed in with drinking water or vegetables and intake of radiation that was re-concentrated in milk from cows (or goats) feeding on grasses contaminated by radioactive fallout (principally applicable to radioactive iodine).

【2】 Radiation effects on human health: Acute deaths and acute effects

Acute deaths

Acute deaths are typically defined as deaths occurring by the end of December 1945 and attributable to the two atomic bombings in August of that year. Numbers of acute deaths are estimated to have been more than 110,000 in Hiroshima and more than 70,000 in Nagasaki.[1] The closer victims were to the hypocenter, the higher the percentage of acute deaths attributable to traumas and burns caused by buildings collapsed in the blast and subsequent fires. At the same time, the closer victims were to the hypocenter, the higher the radiation dose received, making it difficult to distinguish deaths due to radiation from deaths attributable to traumas and burns. To exclude deaths from traumas and burns, RERF studies focus mainly on delayed deaths considered to be attributable to radiation.

The probability of dying directly from radiation exposure depends on the dose received. A commonly used index is the dose at which 50% of a population dies (LD_{50} = lethal dose, 50%). At around the LD_{50} level, bleeding and infection due to immunodeficiency resulting from depletion of hematopoietic stem cells in bone marrow are the main causes of death. Such deaths peaked at about one month after exposure due to the bombings. Recovery sufficient to prevent death typically occurred within two months.

Early estimates based on survivor interviews calculated the LD_{50} in terms of distance from the hypocenter at which 50% of people survived to be 1,000–1,200 meters in Hiroshima and 1,000–1,300 meters in Nagasaki. Relating those distances to exposure dose was not possible at that time, however, because of insufficient shielding information. Later analyses of extensive records at RERF were able to make estimates of shielding, and a bone marrow $LD_{50/60}$ (radiation dose of 50% mortality within 60 days) was calculated to be 2.7–3.1 Gy (with the Dosimetry System 2002 [DS02], the corresponding doses are 2.9–3.3 Gy). These data originated from about 7,600 survivors in 2,500 households exposed inside Japanese houses located within 1,600 meters of the hypocenter in Hiroshima.[2] Survivors inside such houses received special scrutiny, because the homogeneity and ubiquity of the structures allowed for better estimation of individual radiation doses.

Based on this information from A-bomb survivors, together with other information from cases involving exposure to accidental radiation or radiation therapy, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has estimated the bone marrow $LD_{50/60}$ at around 2.5 Gy when no medical assistance is available and ≥5 Gy when adequate medical care is possible.

Acute effects

Symptoms collectively called "acute radiation syndrome" occur within a few hours to months after exposure to high-dose radiation (from approximately 1–2 Gy to 10 Gy). The principal signs and symptoms include vomiting within a few hours, followed within days to weeks by diarrhea, reduced blood cell counts, bleeding, hair loss (epilation), and temporary male sterility. Diarrhea results from damage to cells lining the intestines, reduction in blood cells results from death of hematopoietic stem cells in bone marrow, and bleeding results from declining blood platelets generated from such stem cells. Hair is lost due to damage to hair-root cells. Individual strands of hair do not fall out but rather become thinner and eventually break off. Sterility occurs in men from damage to sperm-generating stem cells.[3]

Except for vomiting, these signs and symptoms are closely related to frequency of cell division, rapid cell division being more sensitive to radiation than slow cell division (e.g., muscle and nerve cells are examples of slowly dividing cells). If the radiation dose is low, this acute radiation syndrome will seldom if ever occur. Conversely, if the dose is high, death can occur within 10–20 days after exposure due to severe damage to digestive organs, or within one or two months after exposure mostly from bone marrow failure.

Figure 1 shows the association between the percentage of those with severe epilation (loss of more than 2/3 of scalp hair) and radiation dose.[4] Although there is only a small effect up to 1 Gy, epilation increases sharply with dose thereafter. (Above 5 Gy, the declining frequency seen in the figure is considered to reflect errors due to overestimation of dose.)

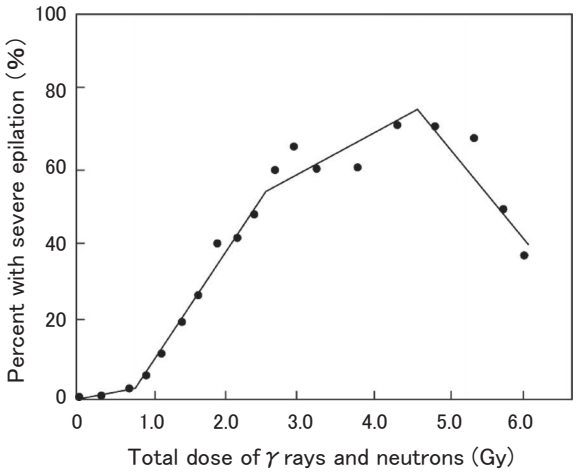


Figure 1. Severe epilation and radiation dose[4]

【3】 RERF study cohorts and study methods

【A】 Study subjects and establishment of study populations

Late radiation effects are not radiation-specific symptoms, and therefore, it is generally difficult to discern whether observed events are attributable to radiation. For this reason, to study late effects from radiation, it is necessary to conduct an epidemiological study that follows a fixed population of exposed individuals in order to observe whether an excess of specific events is occurring in the population in a dose-dependent manner. The Atomic Bomb Casualty Commission (ABCC), the predecessor to the Radiation Effects Research Foundation (RERF), established a follow-up cohort, called the Life Span Study (LSS), based on data from a survey of A-bomb survivors conducted at the time of the 1950 Japan national census. Cohorts of individuals exposed *in utero* and children of A-bomb survivors (F_1) were established based on birth registration records and the results of surveys conducted by ABCC (Table 1). For each study cohort, individual radiation doses were assessed, and follow-up studies have been conducted focusing on mortality, cause of death, and cancer incidence as indices of radiation effects. For subsets of the cohorts, information about health status has been obtained through health examinations carried out at ABCC-RERF.

1. A-bomb survivors

(1) Life Span Study (LSS) cohort

At the inception of ABCC, studies were conducted based on cohorts established independently by individual research scientists. As a result, these studies lacked consistency and continuity. The Francis Committee, convened in 1955, strongly recommended that ABCC develop integrated research protocols with a central focus on three platform protocols based on fixed cohorts. As a result, using data from the supplemental survey of A-bomb survivors conducted in conjunction with the 1950 Japan national census, a fixed population of A-bomb survivors, the LSS cohort, was established to follow mortality in the survivor population. The supplemental A-bomb survivors survey at the time of the 1950 census identified approximately 284,000 A-bomb survivors throughout Japan (excluding Okinawa and Amami Oshima). Of this total, nearly 200,000 survivors were residing in one of the two cities at the time of the census. These 200,000 survivors, together with those who were confirmed as not present in either city at the time of the bombings by ABCC, Hiroshima City, and Nagasaki City surveys conducted in the 1950s, formed the basic sample for establishment of fixed cohorts. The survivors in the basic sample were surveyed to obtain information on birth date, permanent domicile, address, exposure conditions, any acute symptoms, and other details. This information formed the basis for selection of the LSS cohort. The initial LSS cohort consisted of Japanese people who were included in this basic sample with permanent domicile in either city of Hiroshima or Nagasaki. The LSS comprises the following four groups: (1) all survivors who were within 2,000 meters of either hypocenter at the time of the bombings (proximally exposed); (2) all survivors who were at 2,000–2,499 meters (semi-proximally exposed); (3) a sample of survivors at 2,500–9,999 meters, matched to group (1) by sex and age (distally exposed); and (4) a sample of persons, age- and sex-matched to group (1) who were at least 10,000 meters from the hypocenter. Group (4) is designated as the "not-in-city" population and includes the early entrants who entered the cities of Hiroshima or Nagasaki within 30 days of the bombings.

The original LSS cohort of 99,382 persons did not include 9,530 survivors located less than 2,500 meters from either hypocenter at the time of the bombings whose permanent domicile was not in either city of Hiroshima or Nagasaki. These 9,530 survivors were

Table 1. Major RERF research programs and population sizes

Life Span Study	120,321
└ Adult Health Study (Directly exposed)	25,379
In Utero Study	3,638
└ Adult Health Study (*In utero* survivors)	1,021
Children of A-bomb Survivors (F_1) Study	
Mortality and Cancer Incidence	76,814
└ F_1 Clinical Study	12,451
Cytogenetic Study	About 16,000
Biochemical Genetic Study	About 24,000
Molecular Genetic Study	About 1,500

added to the LSS cohort in 1968; another 11,409 distally exposed survivors in Nagasaki were added in 1980, expanding the LSS cohort to a total of 120,321 members. This cohort consists of 93,741 survivors who were within 10,000 meters of the hypocenters as well as 26,580 persons who were not in the cities at the time of the bombings. Table 2 shows estimated radiation doses based on DS02 for the 93,741 survivors (as of 2013). Figure 2 shows exposure locations of LSS subjects and estimated radiation doses, information that was obtained from the shielding history and other surveys (on page 12).

Almost all survivors who were within 2,500 meters of the hypocenters at the time of the bombings are included in the current LSS cohort as the basic sample; however, excluded from the basic sample were survivors who were not residing in either city of Hiroshima or Nagasaki at the time of the October 1950 Japan national census (approximately 30% of those who indicated in the 1950 census that they had been exposed to the atomic bombings), survivors who did not respond to the A-bomb survivors survey, and foreign national survivors.

(2) *In utero* cohorts

Two *in utero* cohorts were established using different sampling methods, one for a mortality follow-up study and the other for a clinical study. The mortality follow-up cohort consists of children who were born during the period from the dates of the atomic bombings (August 6 in Hiroshima and August 9 in Nagasaki) to May 31, 1946, based on three information sources: the 1945–1946 birth registration survey, ABCC's basic roster, and an A-bomb survivors survey conducted at the time of the 1960 national census. This cohort, totaling 2,802 persons, consists of the following five groups: (1) all survivors exposed *in utero* whose mothers were within 1,500 meters of the hypocenters; and samples of individuals matched to (1) on information source, city, sex, and birth month whose mothers were at (2) 1,500–1,999 meters; (3) 2,000–2,999 meters; (4) 3,000–9,999 meters; and (5) individuals who were not exposed *in utero*.

The clinical study cohort consists of survivors who were born during the period from the dates of the atomic bombings until the end of April 1946, resident in either city of Hiroshima or Nagasaki in 1950, and who belong to one of the following three groups: (1) survivors exposed *in utero* whose mothers were within 2,000 meters of the hypocenters, (2) survivors exposed *in utero* whose mothers were at 3,000–4,999 meters of the hypocenters, and (3) individuals who were not exposed. All eligible survivors were included in group (1). For groups (2) and (3), a similar number of members were selected for each group by matching them to group (1) by city, sex, and birth month. This clinical study cohort comprises a total of 1,606 members, of whom a subset of 1,021 was incorporated into the Adult Health Study (AHS) program in 1978.

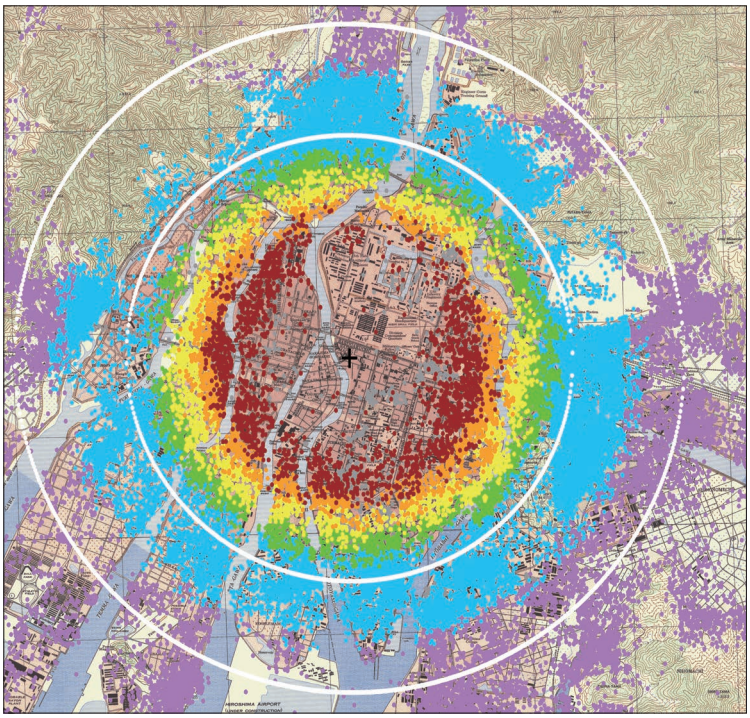
There is some overlap between these *in utero* cohorts. At present, a total of 3,638 individuals from these two cohorts are being followed for mortality.

(3) Adult Health Study (AHS) cohort

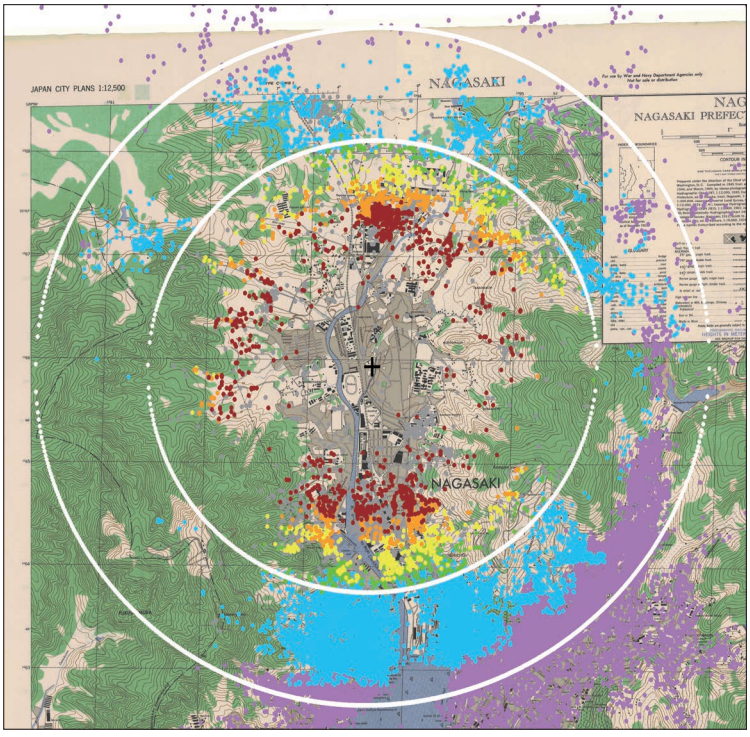
The AHS cohort was established to collect disease incidence and other health information. The AHS

Table 2. LSS subject numbers by estimated radiation dose (DS02, as of 2013)

Weighted absorbed colon dose (Gy)	LSS subjects		
	Hiroshima	Nagasaki	Total
<0.005	21,713	16,823	38,536
0.005–0.05	17,207	6,227	23,434
0.05–0.1	5,537	1,005	6,542
0.1–0.25	6,273	1,270	7,543
0.25–0.5	3,842	956	4,798
0.5–1.0	2,376	1,052	3,428
1.0–2.0	1,151	614	1,765
>2.0	436	189	625
Dose unknown	3,449	3,621	7,070
Total survivors	**61,984**	**31,757**	**93,741**
Not in city (early entrants)	3,792	827	4,619
Not in city (late entrants)	16,438	5,523	21,961
Total not in city	**20,230**	**6,350**	**26,580**
LSS total	**82,214**	**38,107**	**120,321**



Hiroshima



Nagasaki

Figure 2. Distribution of exposure doses of A-bomb survivors in the LSS cohort
The points indicate exposure locations and estimated radiation doses for 93,741 A-bomb survivors excluding persons who were not in the cities at the time of the bombings among 120,321 LSS subjects. The circles on the maps indicate distances of 2 km and 3 km from the hypocenters.

provides clinical and epidemiological information that cannot be obtained from studies of cause of death and cancer incidence in the LSS cohort. The main objectives are to follow health status regarding noncancer diseases (benign tumors, cardiovascular diseases, and other chronic illnesses), through blood test results, and the like, and to elucidate the association between these data and radiation exposure, as well as the underlying mechanisms of diseases associated with radiation and other risk factors.

When established in 1958, the AHS cohort comprised four groups drawn from the original LSS: (1) 4,998 survivors who were within 2,000 meters of the hypocenters and exhibited acute symptoms; (2) 4,975 survivors who were within 2,000 meters of the hypocenters but did not exhibit any acute symptoms; (3) 4,988 survivors at 3,000–3,499 meters from the hypocenter in Hiroshima and 3,000–3,999 meters in Nagasaki; and (4) 5,000 persons not in the cities at the time of the bombings. All eligible survivors were included in group (1). For groups (2) through (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 undergone several expansions. First, the AHS cohort was augmented in 1977 by (1) all 1,185 surviving LSS members with assigned tentative 1965 dose (T65D) (refer to page 12) estimates of ≥1 Gy who were not included in the original AHS cohort and (2) 1,251 sex- and age-matched survivors with assigned T65D dose estimates of <1 Gy. The second expansion in 1978 added (3) 1,021 survivors exposed *in utero* (from the *in utero* clinical study cohort) to the AHS cohort. In 2008, the AHS cohort was again expanded by (4) 1,961 living LSS members who were exposed at the age of less than 10 years, resident in either city of Hiroshima or Nagasaki, and not included in the existing AHS cohort. The total number of AHS members to the present is 25,379; health examinations of 5,000 persons in this group who were not in the cities at the time of the bombings were terminated in 1977.

2. F_1 (children of A-bomb survivors) cohorts

(1) Genetics study cohort

The search for evidence of genetic effects in the children of survivors was a primary focus of early ABCC research. First, an interview survey was carried out during the period 1948–1954 with pregnant women who had applied for a special provision of food rations for women at least 20 weeks into pregnancy, for the purpose of collecting information on the exposure conditions of parents of the unborn children. Based on the information obtained, a combined total of about 77,000 newborns in Hiroshima and Nagasaki were studied for birth defects and early deaths. Subsequently, in 1962, a sex-ratio study was conducted with approximately 71,000 newborns.

(2) Mortality study cohort

Based on the need for continued follow-up of survivors' children, a mortality study cohort was also established. Of 180,600 children (this figure represents a total of the members of the two genetic studies, and about 33,600 persons born between May 1946 and the initiation of the aforementioned studies who were identified on the basis of birth registration records), individuals who met the following three conditions were selected for this study: (1) born between May 1946 and December 1958; (2) place of residence of parents at birth of their children was in either city of Hiroshima or Nagasaki; and (3) exposure conditions of parents were known. Of those selected, a basic mortality study cohort of 53,519 children of A-bomb survivors was established by selecting the following groups of people on the condition of single birth: a) all eligible children with at least one parent within 2,000 meters of either hypocenter at the time of the bombings, constituting the core group; b) children with at least one parent exposed between 2,500 and 9,999 meters; and c) children with neither parent within 10,000 meters. Groups b) and c) each consists of sex- and age-matched groups of children in numbers similar to the number included in the core group.

Subsequently, selected from the expanded LSS cohort members ≤34 years old at the time of the bombings were: i) all eligible persons whose T65D dose estimates are ≥0.1 Gy; and ii) the same number of persons as group i) whose T65D dose estimates are ≥0 Gy and <0.1 Gy. Among the children of these selected individuals, 23,295 persons born between January 1959 and December 1984 were included in the expanded study cohort. As a result, a fixed cohort of 76,814 children of A-bomb survivors was established and has been followed for mortality.

The mortality study cohort did not include 11,667 children who did not meet all the required conditions. These children were, however, born between May 1946 and December 1958 and satisfied the following three conditions at the time of the survey: (1) both their parents were alive; (2) they lived in the so-called catchment area; and (3) they were junior-high-school age or older. They were enrolled only in the cytogenetic study or the biochemical genetic study.

(3) Clinical study cohort

A clinical study of children of A-bomb survivors

was planned in order to investigate genetic effects in adult-onset multifactorial diseases (diseases with complex, or multi-causal, etiologies including life-style factors) among children of A-bomb survivors. The study consists of the Health Effects Study of the Children of A-bomb Survivors, which was the initial study, and the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors, which was conducted as a continuation of the initial study.

i) Health Effects Study of the Children of A-bomb Survivors

The Health Effects Study of the Children of A-bomb Survivors consists of (a) a mail survey and (b) a clinical health study conducted during 2002–2006. The subjects of the mail survey conducted before the clinical health study were selected as follows. Of those who had a permanent domicile in either city of Hiroshima or Nagasaki and maintained a current address in Hiroshima or Nagasaki cities or the surrounding areas, individuals satisfying the following four conditions were selected: 1) at least one parent was exposed to ≥5 mGy (estimated with the Dosimetry System 1986 [DS86]); 2) one parent was exposed to ≥1 Gy, regardless of the other parent's exposure conditions; 3) both parents were known to be survivors, with estimated DS86 doses unknown; or 4) both parents were exposed to less than an estimated DS86 dose of 5 mGy or not exposed. For group 4), subjects were matched to groups 1) through 3) by sex, city, and birth year. Thus, a total of 17,698 persons, as indicated in 1)–4) above, were first selected for the mail survey. In addition, the cohort was augmented by the following two groups of people: 5) 6,785 persons with one parent exposed to an DS86 estimated dose of 5–999 mGy and the other parent either with unknown exposure conditions or without DS86 dose estimates, and who had both permanent domiciles and current addresses in either city of Hiroshima or Nagasaki or the surrounding areas; and 6) 190 persons with current addresses in either city of Hiroshima or Nagasaki or the surrounding areas, with one or both parents exposed to DS86 estimated doses of ≥1 Gy, but were not included in the original mail survey cohort because their permanent domiciles were not in either city of Hiroshima or Nagasaki. As a result, the mail survey mentioned in (a) above was conducted for a total of 24,673 persons during 2000–2005. Of the 14,145 mail survey respondents who expressed their willingness to participate in the subsequent health examinations, 11,951 persons actually did participate in the clinical health study mentioned in (b) above, which was conducted from 2002 until the end of September 2006.

ii) Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors

To follow up on the results from the clinical health study conducted initially, the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors was initiated in 2010. Of the 14,145 persons who expressed their willingness to participate in the health examinations of the Health Effects Study of the Children of A-bomb Survivors, 12,451 individuals (as of 2013) who were alive and had a known address at the initiation of the study are scheduled for participation in the longitudinal follow-up study.

【B】 Study methods

To assess the health effects from A-bomb radiation exposure in the mortality study cohorts of the LSS, *in utero* survivors, and children of A-bomb survivors, information on death and cause of death was obtained to follow these cohorts starting in 1950 based on permission from the Japan Ministry of Justice and Ministry of Health, Labour and Welfare. In addition, information on cancer incidence has been collected from local tumor registries (local cancer registry programs of the governments of Hiroshima City and Nagasaki Prefecture). These registry programs started in 1957 in Hiroshima and 1958 in Nagasaki. For procurement of such cancer incidence data, an application is filed with the primary organization involved in each registry program for use of the data. After the application is reviewed and permission is granted, the registry data are collated with the information from the aforementioned study cohorts to collect cancer incidence data of the cohort members. With regard to leukemia and other hematological disorders, collation is also made with incidence data from leukemia registries established in the 1940s by physicians and others at Hiroshima and Nagasaki universities and hospitals, with leukemia incidence studied since the 1950s. Five questionnaire surveys were carried out between 1965 and 2013 for the LSS cohort members in order to obtain information regarding lifestyle (e.g., smoking, drinking), social environment, and health status. By using information on such risk factors other than radiation exposure, ever more accurate assessment of the association between A-bomb radiation and health effects is being carried out.

The AHS cohort has undergone biennial health examinations, including physical examinations, anthropometric measurements, electrocardiogram testing, chest X-ray examinations, and basic hemato-

logical examinations such as blood cell counts since the AHS began in 1958. Starting in the 1980s, more detailed hematological tests and ultrasound and other such specialized examinations have been added to the list of health examination items. As of March 31, 2013, nearly 60 years after establishment of the AHS cohort, 9,178 persons (about 36%) of all AHS cohort members (25,379 persons) were still alive. Between 70% and 80% of the AHS cohort members residing within the catchment area, i.e., the cities of Hiroshima and Nagasaki and their surrounding areas, participate in the health study program.

With respect to the clinical studies of children of A-bomb survivors, a) the Health Effects Study of the Children of A-bomb Survivors (prevalence study) was conducted over seven years starting in 2000 as the starting point for the study of the association between parental radiation exposure and prevalences of adult-onset multifactorial diseases (hypertension, hypercholesterolemia, diabetes, angina pectoris, myocardial infarction, and stroke) in the children; and b) the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors (incidence study) was initiated in November 2010 to clarify the association between parental radiation exposure and disease development among the children through quadrennial health examinations. As is the case with the AHS, the health examination items include physical examinations, anthropometric measurements, electrocardiogram testing, hematological examinations, urine testing, fecal occult blood testing, chest X-ray examinations, ultrasound examinations, and gynecological examinations.

【4】 Radiation dosimetry

【A】 Physical dose measurements

1. Dosimetry systems and residual radiation

(1) Individual dose estimates

RERF, over many years, has conducted health effects studies based on fixed cohorts of A-bomb survivors. In addition to health effects studies, estimates must be made of individual doses and organ-specific doses for the study subjects to analyze associations between observed health outcomes and radiation doses. For this reason, the estimation of radiation doses constitutes one of the core research aims of RERF. A dosimetry system is used to estimate radiation doses to which individuals were exposed.

There were two types of exposures to A-bomb radiation: one was exposure to initial radiation released at the time of the detonations of the bombs, and the other was exposure to residual radiation, which happened later. Initial radiation, also known as direct radiation, is classified into primary radiation emitted at the time of the detonations of the bombs, and radiation emitted as a result of secondary nuclear reactions inside the fireballs generated by the detonations. Initial radiation consisted mainly of neutrons and γ rays to which people were exposed over a very short period of time, within a few seconds to several tens of seconds, when such radiation reached the body's surface (external exposure).

As explained below, it would be nearly impossible to obtain information required for estimating residual radiation doses. For this reason, only individual whole-body and organ doses from initial radiation are estimated using the dosimetry systems.

With regard to induced residual radiation, individual radiation doses can in principle be estimated because temporal and geographical distributions of radiation in the environment are generally known due to actual measurements and complementary calculations. For such estimation, however, it is essential to obtain accurate records of individual behavior and activity by elapsed time concerning location and duration of stay until at least one week after the A-bombings, during which time induced radiation levels were significantly high. However, more than 10 years after the A-bombings at the initiation of the LSS, it was almost impossible to obtain reliable information for the entire subject population to create dose estimates of adequate quality regarding induced radiation.

For residual radiation due to radioactive substances scattered in the air, the geographical distribution was not uniform, and movement of fallout due to wind and/or water runoff after it had reached the ground makes such distribution more complex. Further complicating the estimation of radiation doses, little is known about the geographical distribution of fallout radiation by elapsed time, except for some measured cases. For that reason, the estimation of dose is extremely difficult. It is not an exaggeration to conclude that the estimation of amounts of inhalation of radioactive substances in the air and intake from food and drink (internal exposure) is nearly impossible.

The only methods for estimation of internal exposure are thus actual measurements using whole-body counters and biological monitoring such as chromosome tests and measurements of tooth enamel by electronic spin resonance (ESR). These tests, however, have limitations in application and involve somewhat limited accuracy. As for biological monitoring, the collection of samples used in the monitoring process is possible only while the survivors are still alive, and exposure to doses of ≤200 mGy cannot be detected accurately. Moreover, while a whole-body counter assesses internal exposure at the time of measurement so that radiation attenuation with time has to be taken into consideration, biological monitoring evaluates the combined effect of both external and internal exposure doses accumulated by the time of measurement.

(2) Principles of dose estimation from initial radiation

Information required for estimating radiation doses comprises: 1) output of A-bomb radiation, 2) attenuation of radiation as it reached individual survivor locations at the time of the A-bombings (distance from the hypocenter), and 3) shielding conditions determined on the basis of the circumstances surrounding exposure to A-bomb radiation of individual survivors. To obtain such information, several projects were carried out including the Ichiban Project, which conducted actual measurements during atomic testing in the desert of the U.S. state of Nevada. In the Ichiban Project, output of the A-bombs, attenuation in the air, and shielding effects from houses were measured. Shielding effects in particular were measured using Japanese houses that had been constructed with standard building materials commonly used at the time of the bombings. Computer simulation was carried out to calculate radiation transport based on actual measurements.

Since such information on exposure and shielding conditions of individual survivors was essential for calculating radiation attenuation, a series of surveys using various questionnaires as indicated in the next section were conducted by visiting and interviewing individual survivors.

(3) Survey of exposure status for individual survivors

Estimates of individual radiation doses depend on information about exposure conditions of individual survivors. This information includes survivor location (distance from the hypocenter); presence or absence of shielding between a survivor and the hypocenter, such as terrain (e.g., hill) and concrete buildings; whether indoor or outdoor; location inside a house (distance from a window and/or other opening in a wall); body orientation (standing, sitting, facing toward the hypocenter or not); and whether the survivor was a child or an adult at the time of exposure. For this purpose, five different home-visit and interview surveys of individual survivors were carried out between 1949 and 1965. The surveys are summarized below.

1) 1949 Radiation Census

The 1949 Radiation Census field survey was carried out between 1949 and June 1953 by means of interviews conducted with about 86,000 people in Hiroshima and about 95,000 people in Nagasaki. This Radiation Census yielded information related to personal identification (e.g., name and birth date), exposure conditions (location, shielding, posture, distance, and coordinates), addresses at the time of the A-bombings and at the time of this survey, and survivors' occupations.

2) Radiation Questionnaire

The Radiation Questionnaire replaced the 1949 Radiation Census and was conducted from June 1953 to the end of 1955 to investigate radiation damage in more detail. The survey was conducted with about 26,000 people in Hiroshima and about 14,000 people in Nagasaki to obtain information related to personal identification, exposure conditions, traumas and burns as they pertained to A-bomb-related symptom history, menstruation, onset of disease after the A-bombings, and survivors' health status at the time of the questionnaire.

3) Migration Questionnaire

The Migration Questionnaire was conducted between 1955 and January 1956 with about 26,000 people in Hiroshima and about 24,000 people in Nagasaki to obtain information related to subjects, conditions at the time of the questionnaire, exposure conditions, individual(s) that accompanied the survivor at the time of the A-bombings, circumstances surrounding the survivor's entrance into the city limits, past and current addresses, and exposure conditions of family members.

4) Master Sample Questionnaire

The Master Sample Questionnaire was conducted from April 1956 to November 1961 with about 138,000 people in Hiroshima and about 23,000 people in Nagasaki to obtain necessary information for establishment of the master sample. Information was obtained pertaining to subjects, exposure conditions, individual(s) that accompanied the survivor at the time of the A-bombings, past and current addresses, exposure conditions of family members, A-bomb-related symptom history, other symptoms, menstruation, and health status at the time of the questionnaire. This questionnaire is a compilation of the Radiation Questionnaire and the Migration Questionnaire.

5) Shielding History

To obtain shielding information to be used as a basis for calculation of estimated radiation doses, three different types of drawings were prepared from February 1954 to August 1965: layout drawings indicating accurate survivor location; floor plan drawings on a scale of 1:100 depicting location, posture, orientation relative to the burst point, and shielding objects inside a house; and cross-sectional drawings generated using a perspective projection method based on the floor plan drawings. These drawings were prepared for everyone within 1,600 m and 30% of those who were at distances of 1,600–1,999 m from the hypocenter in Hiroshima, and everyone within 2,000 m in Nagasaki. There are about 20,400 such drawings for Hiroshima and 8,500 for Nagasaki.

Of these five survey instruments, the Master Sample Questionnaire of 4) above is the most comprehensive and the Shielding History of 5) is the most detailed.

(4) History of the dosimetry systems

The dosimetry systems to estimate individual radiation doses based on the information collected through the five surveys described above have been revised four times and thereby substantially improved (the two-digit number in each name denotes the year of publication):

T57D This tentative dosimetry system was rarely used.

T65D This dosimetry system, an improved version of T57D, was developed on the basis of actual measurements obtained from the Ichiban Project.

DS86 As computers became available with sufficient power to conduct a simulation of the kinetics of neutrons and γ rays with consideration for shielding by structures and the human body, this highly accurate system allowed calculation of radiation doses received by 15 different organs of each survivor by the addition of information such as

survivor's location, shielding conditions, and body position and orientation at the time of the A-bombings.

DS02 After DS86 was adopted for use, it was suggested that some of the calculations did not match the neutron activation measured in samples of materials in Hiroshima, especially beyond 1,500 m from the hypocenter. DS02 was developed to resolve this and other issues. The discrepancy between the calculations and measurements of neutrons beyond 1,500 m was resolved by raising the bomb's burst height by 20 m. Due to improved measurements of neutron activation of building materials collected subsequently, good agreement was achieved between the calculations and measurements up to 1,500 m from the hypocenter.

Currently, RERF uses DS02 to assess health effects from radiation for the LSS, AHS, and other studies. The number of LSS subjects by exposure dose is shown in Table 2 (refer back to page 6).

(5) Effects of residual radiation on risk assessment of A-bomb radiation

RERF has published radiation-risk information showing associations between radiation dose and frequency of cancer development (and mortality) based on its LSS of 120,000 people, including A-bomb survivors. These data are highly regarded internationally and used as basic data for the establishment of radiation protection standards. For these risk calculations, only doses from initial radiation have been used. If the residual radiation exposures were too large to be ignored, the reliability of these risk data would decrease in proportion to the amount of unknown residual radiation levels. As stated below, however, there is reason to believe that the effects of residual radiation were low enough to be considered virtually negligible.

1) RERF researchers and many other scientists have worked on analyses of radiation doses from the A-bombs dropped on Hiroshima and Nagasaki. In particular, Chapter 6 of the DS86 report[5] summarizes the results of area radiation surveys conducted within several years after the A-bombings. Most were conducted from August through November of 1945, some even before the typhoons that devastated Hiroshima. A major importance of these studies lies in the fact that the measurements were made before the nuclear tests conducted in various parts of the world contaminated the entire planet with radioactive fallout. After this contamination it was very difficult or impossible to accurately measure amounts of residual radiation from the 1945 atomic bombings. But such studies have indicated that the residual radiation levels fell within the estimated range of error of the initial radiation doses.

2) As mentioned above, the geographical distribution of induced radiation dose by elapsed time after the A-bombings is known. Thus, simulation of such radiation doses has been performed, assuming various circumstances concerning individual behavior and activity immediately after the A-bombings. Table 3 provides examples of dose estimates for early entrants into areas near the hypocenters. The table assumes that a person had spent a considerable amount of time very close to either of the hypocenters within the first several days after the bombings. For example, if someone had stayed at a distance of 500 m from one of the hypocenters for 12 hours on the day following the A-bombing, the induced radiation doses would have been about 15 mGy in Hiroshima and 3 mGy in Nagasaki. On the other hand, if a person had stayed at a distance of 1,000 m from the hypocenter, the doses

Table 3. Potential exposures of early entrants, Hiroshima and Nagasaki

Time of entry[a]	Distance from hypocenter and weighted absorbed colon doses (mGy)				
	200 m	500 m	700 m	1,000 m	1,500 m
Hiroshima					
Day 2[b]	82	15	3	<0.5	<0.5
Day 3	40	8	2	<0.5	<0.5
Nagasaki					
Day 2	18	3	1	<0.5	<0.5
Day 3	9	1	<0.5	<0.5	<0.5

[a] The table dose estimates assume that a person arrived at the indicated distance from the hypocenter at 6:15 a.m. and stayed at that location for a full 12 hours.

[b] Day 2 refers to the day after the bombing, and day 3 is the next day. For days 4, 5, and thereafter, dose levels for each successive day decreased by approximately 50% from the previous day.

would have been inconsequential.

3) One report by NHK (Japan Broadcasting Corporation; Japan's national public broadcasting organization) recounts a study of Japanese Kahoku military troops that serves as an example of an actual study of a group of people exposed to residual radiation.[6] These special duty troops consisted of about 250 reservists gathered from the city of Higashi-Hiroshima for relief activities, such as clean-up of rubble near the hypocenter, starting August 7, the day following the A-bombing, through August 13. RERF, Hiroshima University, and other organizations cooperated with each other to calculate radiation dose estimates for a Kahoku unit consisting of 99 reservists for whom precise behavior and activity records during that period were maintained. Data showed that most of the radiation exposure among these individuals was from induced radiation, that the estimated maximum dose was 100 mGy based on both chromosome aberration frequencies and computer simulations, and that the average dose for the entire unit was 13 mGy. Moreover, a mortality study of these 99 reservists conducted over a 42-year period starting in August 1945 showed no difference in either category of all causes of death or cancer when compared with national averages.

4) Other examples of studies of residual radiation exposure include a study of cause of death among early entrants into the cities conducted as part of the LSS. This study of cause of death was conducted during 1950–1978 with 4,512 people who entered the cities of Hiroshima and Nagasaki within one month after the A-bombings. Results showed no evidence of an increase in mortality due to either all causes of death or cancer. In view of the fact that people could not approach the areas near the hypocenters because of secondary fires on the day of the A-bombings, the radiation doses of the abovementioned Kahoku troops are considered to be the maximum plausible levels of residual radiation exposure.

5) Studies concerning internal exposure include investigations conducted in collaboration with Dr. Shunzo Okajima and other researchers from Nagasaki University in 1969, 1970, and 1971 on subjects in the Nishiyama district of Nagasaki, where the amount of radioactive fallout was the largest of any location in either Nagasaki or Hiroshima.[7] Interviews were first conducted with residents whose radiation doses were considered to be the highest in this district, and then 50 residents whose internal exposure doses were considered to be the highest due to their intake of local produce and drinking water were selected as subjects. Nishiyama residents received a small, continuous radiation dose from the Nagasaki A-bomb's fallout radioisotope cesium 137 (Cs-137; the principal isotope, with a physical half-life of 30 years) due to the intake of local agricultural products. The related level of Cs-137 declined over time in soils where crops were grown with a half-life of about seven years, which resulted from the physical half-life decay and the environmental erosion from the soil of minerals carrying the isotope. It was shown by whole-body counter measurements of internal exposure doses (Cs-137) that the cumulative exposure doses during the 40 years of 1945–1985 could be estimated at 100 μGy for males and 80 μGy for females. Those cumulative doses were calculated on the basis of a half-life of 7.4 years, which was inferred from additional measurements conducted on a portion of the relevant population in 1981. Those low levels (i.e., 100 and 80 μGy) represent only about 1/1,000 of the accumulated 40-year global background radiation dose announced by the World Health Organization (WHO).

As previously mentioned, only estimates of initial radiation doses are used for calculation of radiation risks at RERF, but there is considered to be error of about 35% in individual dose estimates based on DS02. The major reason for this uncertainty is thought to be imprecise information obtained from interviews conducted in shielding studies used to estimate radiation doses.

RERF's risk evaluations of cancer incidence and mortality from A-bomb radiation depend largely on the fact that risk estimates among people exposed to high doses of 1–4 Gy show clear radiation-dose response. Risk estimates of people who were exposed to estimated residual radiation doses of about 10–100 mGy would fall within the range of error, making scientific assessment difficult.

Residual radiation doses are thus much lower than

Note: Cs-137 half-lives
Physical half-life: 30 years
Environmental half-life: 7.4 years
Biological half-life: 100 days (biological half-life depends on age of the affected individual, with that in infants and children estimated to be around 30 days). Biological half-life is a measure of the rate at which any single intake of, for example, cesium, radioactive or non-radioactive, is eliminated from the human body by biological processes. It is the major determinant of the equilibrium level when the dietary intake of cesium is continuous.

initial radiation doses, and there is substantial error involved in their estimation. We therefore cannot expect that the precision of risk estimation would improve or the risk estimates would change materially, even were information on residual radiation doses to be added. The numbers of cancer deaths or cancer cases, which are used as the numerators in risk estimation, are values obtained via death certificates and cancer registries independently of radiation dose estimates. Therefore, if radiation doses, which serve as the denominator in the equation, are underestimated because of exclusion of residual radiation, cancer risks would be overestimated. Using such high risks for establishment of radiation protection standards means that the standards would be on the safe side.

2. Biological effects of internal exposure

Residual radiation, particularly internal exposure, has attracted increased attention since the nuclear power plant accident in Fukushima, because of the high frequency of thyroid cancer development among children in Chernobyl as well as for other reasons. In the era of the former Soviet Union, cover-up of radioactive contamination led to more widespread radiation damage among the population. People drank milk from cows that were grazing on radioactive iodine-contaminated grass without realizing that the milk contained high radiation concentrations. In addition, nonradioactive iodine was in short supply for use as a blocking agent to prevent ingested radioactive iodine from being taken up and retained in the thyroid.

Different from external exposure, internal radiation exposure continues as long as radioactive substances taken into the body are not discharged, even when radiation doses decrease in accordance with the physical half-life of such substances. It is therefore important to avoid intake of radioactive substances to the fullest extent possible. However, there is no scientific basis for concluding that internal exposure is more dangerous than external exposure. Both internal and external exposures are believed to contribute to late effects such as cancer development.

It is important to note that level of risk depends on the radiation dose to which cells (probably, tissue stem cells) in which cancers develop are exposed, regardless of whether the exposure is due to external or internal sources. In the case of external exposure, target organ doses are calculated with consideration to shielding effects by the skin and intervening body tissues. In the case of internal exposure, as can be seen in the relationship between the thyroid and iodine, metabolism in the body differs by radioactive nuclide (element), which may cause uneven distribution in the body. With all of these factors taken into account, if the radiation dose of the target organ is the same, the level of risk should be the same regardless of whether the dose is from internal or external exposure. Numerous human studies comparing the cancer effects of internal and external exposures confirm this assertion.[8]

In the case of internal exposure, radiation is emitted radially from radioactive particles taken into the body; the doses near these particles can be very high. However, high radiation dose at a particular site does not necessarily increase cancer risk immediately. Stem cells that are related to carcinogenesis do not exist in organs and tissues uniformly, and therefore if no such stem cells exist in the immediate vicinity of radioactive particles, emitted radiation will only pass by without becoming involved in carcinogenesis. Also, if radiation dose for a target organ is extremely high, cells themselves die, which conversely leads to a downturn in cancer risk. Based on these findings, the International Commission on Radiological Protection (ICRP) is of the opinion that cancer risk due to radiation from radioactive substances taken into the body (i.e., internal exposure) is about the same as risk from external exposure if radioactive substances are distributed evenly throughout the entire body and lower if the radioactive substances are distributed unevenly.

This hypothesis has been proven by the following animal experiment and studies:

- A large, high-quality animal experiment showed that comparable doses of radioactive iodine and X rays caused similar frequencies of thyroid cancer.[9]
- Thyroid cancer risk estimates via radioactive iodine intake in Chernobyl did not show a significant difference from those obtained by studies of external exposures, as can be seen below. At least, it cannot be said that the former is higher than the latter.

1) A combined analysis of five major studies of external exposure to medical radiation and A-bomb radiation reported a relative risk of 8.7 for thyroid cancer after exposure to 1 Gy.[10]
2) Three major studies of the effects of radioactive iodine exposure (internal exposure) among Chernobyl area children reported relative risk estimates at 1 Gy of 6.2, 3.2, and 2.9, respectively.[11–13]

【B】 Biological dosimetry

1. Chromosome aberrations

Chromosomes are comprised of long thin molecules of DNA. When cells are exposed to radiation or other carcinogens, their DNA sometimes breaks, and the broken ends may rejoin in different patterns from their original arrangements. The abnormalities that

result are termed chromosome aberrations and can be observed when cells divide at mitosis. The frequency of chromosome aberrations increases in proportion to the radiation dose to which the cells are exposed, and thus this measure is widely used as a biological dosimeter.

Study of the chromosomes of A-bomb survivors began in 1967 with the objective of evaluating and complementing the physically estimated dose of each A-bomb survivor. By that time, more than 20 years after the atomic bombings, unstable chromosome aberrations, such as the relatively easy-to-detect dicentric chromosomes, had mostly disappeared from the body due to their structural characteristics (half-life of just a few years). For this reason, stable chromosome aberrations, such as translocations, were chosen for study, because though difficult to detect, they change little over time. A study of stable chromosome aberration frequency using the Giemsa staining method was conducted over the course of about 25 years until the end of 1993 to obtain information from approximately 3,000 A-bomb survivors in Hiroshima and Nagasaki (Figure 3).[14] The study results are summarized as follows:

1) Stable chromosome aberrations remained in A-bomb survivors' peripheral blood T lymphocytes even several decades after the A-bombings;

2) The proportion of cells with chromosome aberrations increased significantly with physically estimated doses;

3) Chromosome aberration frequencies were widely dispersed in comparison with physical dose estimates;

4) The slope of the dose-response curve was significantly steeper in Hiroshima than in Nagasaki;

5) The slope of the dose-response curve was significantly lower for those who were exposed inside factories in Nagasaki and those exposed outdoors without any shielding (both cities) than for those who were exposed inside Japanese houses.

Although there are some problems with these results, they do suggest that stable chromosome aberrations can be used to biologically estimate radiation doses even a long time after exposure. Several possible reasons may account for the wide dispersion of chromosome aberration frequencies compared with physical dose estimates, as shown in Figure 3. These reasons include: possible inter-observer variation in detection capability of stable chromosome aberrations, individual differences in radio-sensitivity, effects from medical radiation exposure, errors in physical dose estimates, and errors in information (survivor location and shielding conditions) obtained via interviews used for calculation of physical doses.

In 1994, the analysis method used for the chromosome study was changed from the Giemsa staining method to fluorescence *in situ* hybridization (FISH). FISH is a technique for staining specific chromosomes based on use of DNA probes specific to those chromosomes. With FISH, exchange-type chromosome aberrations, such as translocations, can be detected objectively and efficiently (Figure 4). Since the Giemsa staining method-based studies were conducted at the Hiroshima and Nagasaki laboratories separately, possible effects on the study results from inter-observer variation in detection capability cannot be ruled out. To reduce the possibility of similar inter-

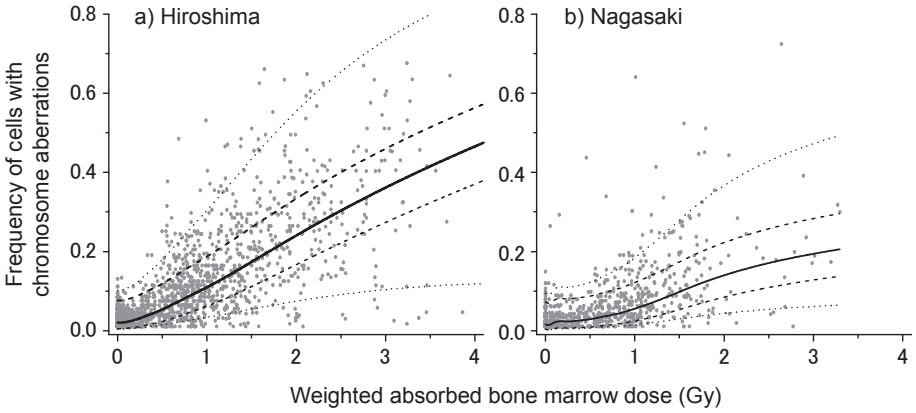


Figure 3. Frequency of cells with stable chromosome aberrations by the Giemsa staining method in relation to physical dose estimates (DS86).[14] Each dot represents individual survivor data (n=1980 in Hiroshima, n=1062 in Nagasaki). The solid line indicates dose-response relationship, the dashed line 95% confidence interval, and the dotted line coefficient of variation of 50% assumed for dose estimates in addition to 95% confidence interval.

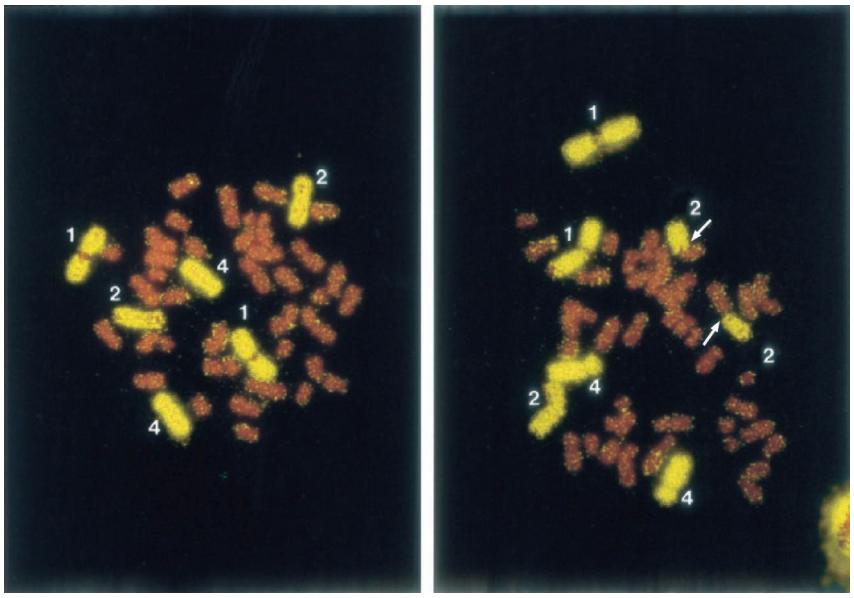


Figure 4. Metaphase stained with FISH. The left metaphase shows a normal cell and the right, a translocation indicated by arrows. Chromosomes 1, 2, and 4 are painted yellow and the other chromosomes are stained red. All translocations between yellow and red chromosomes can thus be detected accurately.

observer variation with the FISH method, a decision was made to carry out all tasks except blood drawing at the Hiroshima Laboratory. It was confirmed that the observed differences between the Hiroshima and Nagasaki results were reduced considerably with the FISH-based analysis results. It is highly likely, therefore, that the city difference observed with the Giemsa staining method was attributable to inter-laboratory variation in capability to detect aberrations. At the same time, dispersion in chromosome aberration frequencies compared to physical dose estimates is still as large with the FISH method as the Giemsa method, with differences in dose response observed depending on shielding conditions.

2. Electron spin resonance (ESR) using tooth enamel

Measuring CO_2^- radicals remaining in tooth enamel is effective for assessing individual radiation dose. Enamel is separated from teeth that have been extracted for medical reasons, and the presence of radicals is quantified using electron spin resonance (ESR) or electron paramagnetic resonance (EPR). Because the ESR signal intensity is linearly correlated with radiation exposure, it can be used as a direct measure of total physical dose, regardless of exposure modality, i.e. acute or chronic exposures. This method is also used for estimating radiation doses in situations like the Chernobyl nuclear accident.

With the ESR method, there initially were concerns

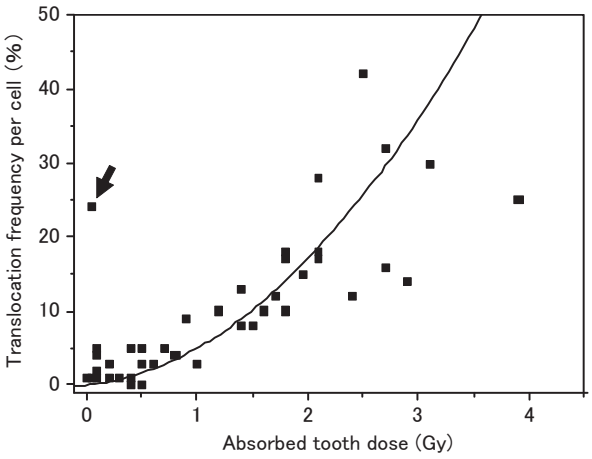


Figure 5. Translocation frequencies in lymphocytes and dose estimates using molars donated by the same survivors.[15] The curve shows a dose-response relationship of dicentric chromosomes obtained from an *in vitro* γ-ray irradiation experiment of lymphocytes (it is believed that dicentric chromosomes and translocations occur at the same frequencies). The arrow indicates a wisdom tooth donated by a survivor exposed to A-bomb radiation at the age of 15. In this case, the absorbed tooth dose was 0 Gy, presumably because the enamel on the tooth had not yet formed at the time (note that there is large variation among individuals in the timing of wisdom tooth development).

about effects from diagnostic dental X-ray exposures, but the following experiment showed that any such effects were insignificant. Diagnostic X rays are usually applied from outside of the mouth. In this experiment, a tooth was divided into a buccal side (outside) and lingual side (inside) for measurement, and there proved to be no difference between these two sides in the case of molars. There were more than a few cases in front teeth, however, in which the ESR signal intensity of enamel separated from the buccal side was considerably larger than that from the lingual side.[15] The difference could not be explained as being caused by diagnostic dental X rays. Possible effects from solar ultraviolet exposure were suggested, but the cause of this particular result has not yet been proven.[16]

Doses estimated using molars donated by 60 A-bomb survivors were compared with measurements of translocation frequencies in blood lymphocytes made from the same donors (Figure 5).[15] The relationship between tooth-based dose estimates and translocation frequencies generally agreed well with a dose-response curve predicted on the basis of *in vitro* irradiation experiments of lymphocytes.

【5】 Radiation effects on human health: Late effects

【A】 Results from studies of A-bomb survivors

RERF periodically publishes reports on study results of mortality and causes of death in the LSS population as well as health examination results in the AHS population. By 2013, 14 LSS reports[17] and 8 AHS reports[18] had been published, in addition to several thousand papers on specialized topics.

According to a report on mortality risk focusing on the years 1950–2003 and tracking 86,611 people with DS02 doses who were in the cities of Hiroshima or Nagasaki at the time of the bombings,[17] an estimated 50,620 people died during this period, and the excess relative risk per Gy (ERR/Gy) was 0.22 (95% confidence interval [CI]: 0.18, 0.26). Table 4 shows the number of deaths observed and estimated excess deaths from solid cancers and noncancer diseases by radiation dose in the LSS.[17] Of the 10,929 deaths from solid cancers and 35,685 deaths from noncancer diseases among LSS subjects with dose ≥0.005 Gy, the excess numbers of cases attributable to radiation are estimated to be 527 and 353, respectively.

Table 5 shows follow-up status by age at exposure among all LSS subjects as of the end of 2008. At that time, 64% of the population had died, but about 70% of those who were exposed under age 20 were still alive.

1. Malignant tumors

(1) Leukemia and related diseases

Increased leukemia incidence was the earliest delayed effect of radiation exposure observed in A-bomb survivors. Although the leukemia risk due to radiation exposure is considered to have started increasing about two years after the A-bombings, the follow-up of the LSS population began in 1950, five years after exposure, with no systematic data obtained prior to that time. It is estimated that the risk increase in the LSS population reached its peak 7–8 years after exposure and then began to decline continuously, but the increased risk does not appear to have disappeared completely even now, more than 50 years later. For those exposed at younger ages, the risk increase was larger and the decline after the peak more rapid (Figure 6).[19] Of the four major leukemia subtypes (acute myelogenous leukemia [AML], acute lymphatic leukemia [ALL], chronic myelogenous leukemia [CML], and chronic lymphatic leukemia

Table 4. Observed and estimated excess deaths from solid cancers and noncancer diseases in the LSS cohort[17]

Colon dose (Gy)	Number of subjects	Person-years	Solid cancers			Noncancer diseases[b]		
			Number of deaths	Number of excess deaths[a]	Attributable fraction (%)	Number of deaths	Number of excess deaths[a]	Attributable fraction (%)
<0.005	38,509	1,465,240	4,621	2	0.0	15,906	1	0.0
0.005–0.1	29,961	1,143,900	3,653	49	1.3	12,304	36	0.3
0.1–0.2	5,974	226,914	789	46	5.8	2,504	36	1.4
0.2–0.5	6,356	239,273	870	109	12.5	2,736	82	3.0
0.5–1	3,424	129,333	519	128	24.7	1,357	86	6.3
1–2	1,763	66,602	353	123	34.8	657	76	11.6
2+	624	22,947	124	70	56.5	221	36	16.3
Total	86,611	3,294,210	10,929	527	4.8	35,685	353	1.0

[a] Estimated number of excess deaths calculated using the fitted model in reference 17
[b] Non-neoplastic blood diseases were excluded from noncancer diseases.

Table 5. LSS follow-up status as of the end of 2008

Age at exposure (years)	Number of subjects	Alive (%)	Dead (%)
0–9	23,717	83.6	16.1
10–19	25,994	63.5	36.2
20–29	15,785	39.1	60.7
30–39	17,310	6.1	93.8
40–49	18,403	0.2	99.8
50+	19,112	0.0	100.0
Total	120,321	36.2	63.6

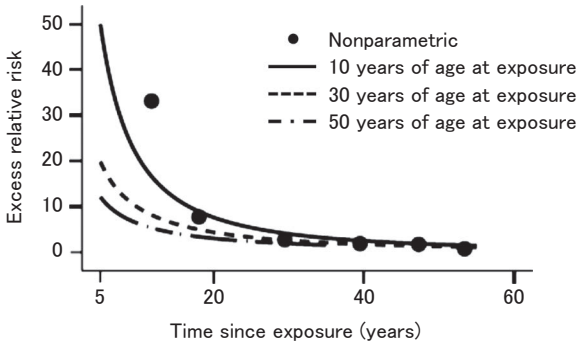


Figure 6. Change in sex-averaged ERR of leukemia (excluding CLL and ATL) as related to age at exposure and time since exposure for people who were exposed to 1 Gy[19]

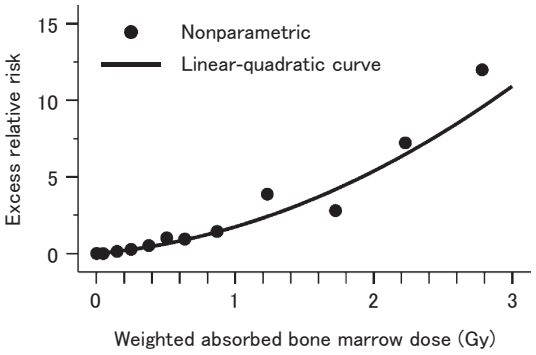


Figure 7. Dose-response relationship of leukemia mortality risk[revised from 19]

[CLL]), risk increases among A-bomb survivors were confirmed for all the subtypes except CLL.[20] It is considered that the risks of these three subtypes reached their peaks 5–10 years after exposure. The risks of ALL and CML then declined continuously, almost disappearing by the 1960s, whereas the risk of AML was found to have persisted even after 2000.[19] No relationship between adult T-cell leukemia/lymphoma and radiation dose was observed.

Results from studies of A-bomb survivors in Nagasaki showed that myelodysplastic syndrome (MDS) was related to exposure distance and radiation dose.[21] Although MDS is a clinical condition that has attracted attention in recent years and requires long-term observation, MDS, like AML, tends to persist over a long period. Thus, especially among those exposed before adulthood, the possibility exists that the risk may continue throughout their lifespan.

With regard to the dose-response relationship between radiation exposure and leukemia risk, it has been shown that a linear quadratic model with concave upward curvature fits better than a linear model. Analysis of incidence during the period 1950–2001 regarding all leukemia (except for CLL and adult T-cell leukemia [ATL], for which no relationship with radiation has been observed[19]) also showed a dose response with concave upward curvature, with a more rapid increase in risk in the higher dose range. The estimated ERR at 1 Gy is 1.74, with a linear term coefficient of 0.79 (95% CI: 0.03, 1.93) and a quadratic term coefficient of 0.95 (95% CI: 0.34, 1.80) for the ERR at age 70, after exposure at age 30 (Figure 7). Because the frequency of AML is the highest among the four major subtypes, the results for all leukemia tend to mirror the results for AML.

Table 6 shows the observed numbers of all leukemia cases except for CLL and ATL, as well as the estimated number of excess cases in the LSS population by bone marrow dose. 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[17] showed significantly elevated risk of malignant lymphoma among males (ERR/Gy =

Table 6. Observed numbers of all leukemia cases excluding CLL and ATL and the estimated number of excess cases in the LSS population[19]

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 using the fitted model in reference 19

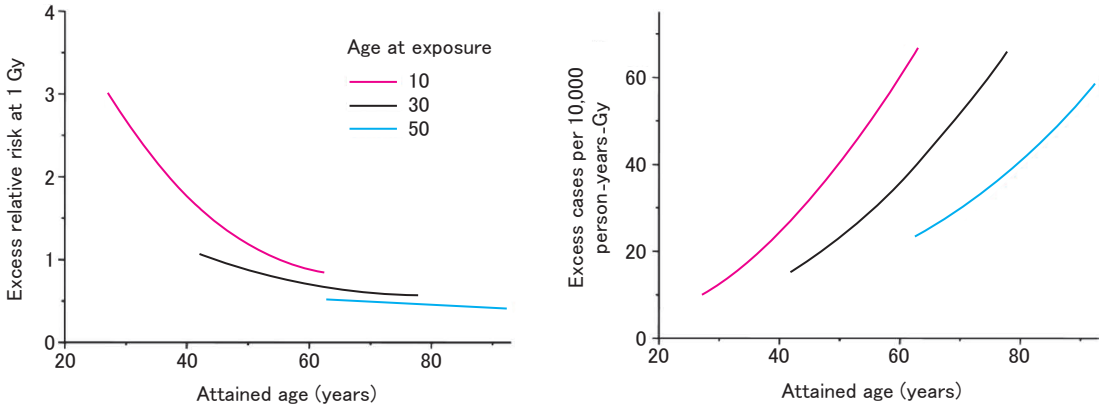


Figure 8. Change in sex-averaged ERR/Gy (left) and EAR per Gy per 10,000 person-years (right) of solid cancer incidence by attained age among those exposed at 10, 30, and 50 years of age[22]

0.70, 95% CI: 0.08, 1.7) but no elevated risk among females (ERR/Gy = –0.18, 95% CI: –0.21, 0.24). In the incidence study,[19] ERR/Gy for non-Hodgkin lymphoma, which accounts for approximately 90% of malignant lymphoma cases in Japan, was also marginally significant among males (ERR/Gy = 0.46, 95% CI: –0.08, 1.29), while no elevated risk was seen among females (ERR/Gy = 0.02, 95% CI: –0.44, 0.64). There is no clear explanation for these differences between males and females.

In the mortality study,[17] ERR/Gy for multiple myeloma was not significant among males (ERR/Gy = 0.11, 95% CI: –0.28, 1.6), but a significant risk was observed among females (ERR/Gy = 0.86, 95% CI: 0.02, 2.5). At the same time, the incidence study[19] showed no significant elevated risk (ERR/Gy = 0.38, 95% CI: –0.23, 1.36) and no sex difference.

(2) Solid cancers

Mortality risk from all solid cancers during the period 1950–2003 has been reported.[17] Because risks of less deadly cancers, such as breast, thyroid, and skin cancers, should be evaluated based on incidence rather than mortality, results of solid cancer incidence studies during 1958–1998[22] will mainly be introduced here. Among 105,427 people who were not in the cities at the time of the A-bombings or for whom DS02 doses have been estimated, and who were alive in 1958 when cancer registries were initiated in Hiroshima and Nagasaki and had not been diagnosed with cancer by then, 17,448 cases of first primary solid cancer were identified during the observation period. Cancer risks among A-bomb survivors vary by sex, age at exposure, and attained age (time since exposure). Figure 8 shows changes of sex-averaged ERR and excess absolute rate (EAR) of all solid cancers by age at exposure in relation to attained age.[22] (Refer to the Glossary on page 47 for definitions of ERR and EAR.) For the same attained age, both ERR and EAR are higher for people with younger age at exposure, suggesting higher radiation sensitivity among young people. ERR decreases with attained age, and the decrease is more rapid among people exposed at younger ages. Among those exposed at older ages, the decrease is small and the ERR is almost constant. As the cancer incidence among unexposed people increases with attained age, EAR increases with attained age.

Radiation doses to which the LSS population was exposed range from extremely low doses to about 4 Gy. The solid cancer incidence study conducted during the period 1958–1998 showed an increase in dose response with radiation in the range of <2 Gy, suggesting a linear relationship. However, this increase became slightly more gradual in the range of ≥2 Gy (Figure 9).[22] The non-linearity was not significant, and the reason for the more gradual increase is unclear, but it may be due to uncertainty in dose estimation or to cell lethality effects (when cancer does not develop

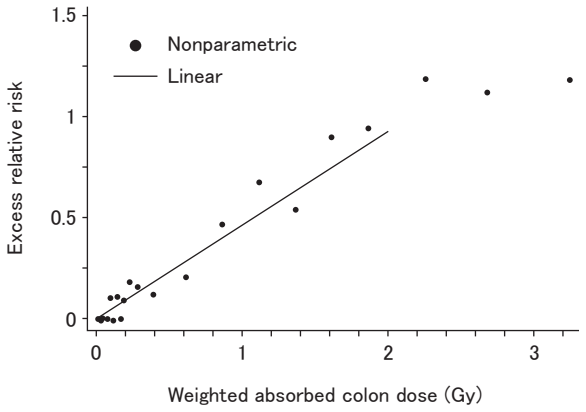


Figure 9. Relationship of ERR of solid cancer incidence to colon dose in the LSS population[revised from 22]

because high doses kill cells). Threshold models, which assume no risk increase below a certain dose, have been assessed, but no significant improvement in the degree of fit has been shown in comparison with linear models, with estimates showing that even were a threshold to exist, it would not exceed 0.085 Gy.

A-bomb survivors have been exposed to other carcinogenic factors besides radiation, such as smoking, and therefore not all cancers experienced by the survivors are caused by A-bomb radiation. That is why it is important to show the degree to which the development of cancer is attributable to A-bomb radiation among the survivors. Table 7 indicates the observed number of all solid cancer cases and estimated excess numbers of cases by radiation dose in the LSS population.[22] It is estimated that 850 of all the 7,851 solid cancer cases among the LSS subjects exposed to ≥0.005 Gy is the excess number related to radiation exposure, with the attributable fraction being 11%. Limiting the subjects to those exposed to radiation of ≥2 Gy, it is estimated that 111 of all the 185 solid cancer cases is the excess number related to radiation exposure, with that attributable fraction being 61%.

Figure 10 shows ERR/Gy of all solid cancer and site-specific cancer incidences adjusted for sex, age, age at exposure, and city and their confidence intervals.[22] As described previously, ERRs change in relation to sex, age at exposure, and attained age. Thus, sex-averaged risks of those whose age at exposure was 30 and whose attained age was 70 are shown hereafter

Table 7. Observed number of solid cancer cases and estimated excess number of cases in the LSS population[22]

Dose (Gy)	Subjects	Person years	Cases	Background[a]	Fitted[a] excess	Attributable fraction
<0.005	60,792	1,598,944	9,597	9,537	3	0.0%
0.005–0.1	27,789	729,603	4,406	4,374	81	1.8%
0.1–0.2	5,527	145,925	968	910	75	7.6%
0.2–0.5	5,935	153,886	1,144	963	179	15.7%
0.5–1	3,173	81,251	688	493	206	29.5%
1–2	1,647	41,412	460	248	196	44.2%
2–4	564	13,711	185	71	111	61.0%
Total	105,427	2,764,732	17,448	16,595[b]	853[b]	10.7%[c]

[a] Estimated number of cases calculated by fitting the model used in reference 22
[b] Because integers are used, the sums of the individual figures do not equal the totals.
[c] Attributable fraction means percentage of estimated excess number of cases in the number of solid cancer cases among those exposed to ≥0.005 Gy.

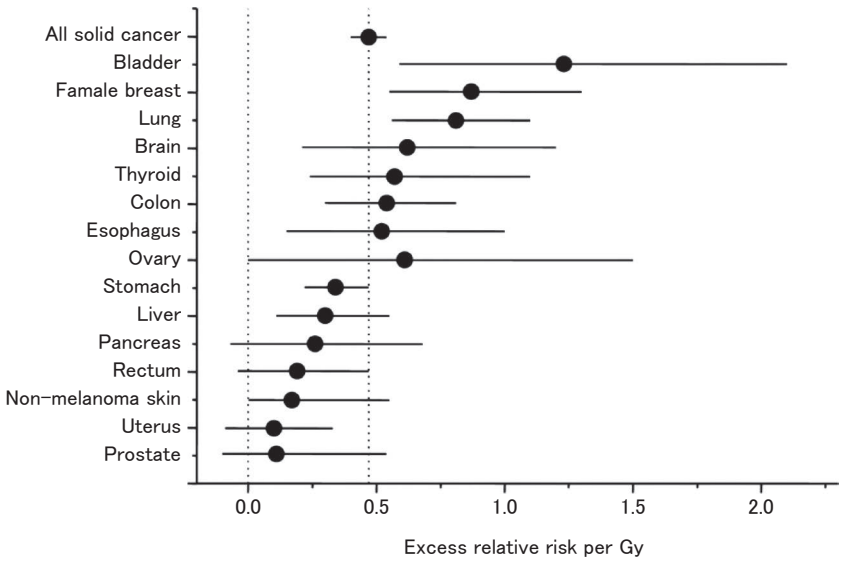


Figure 10. ERR/Gy for the incidence of site-specific cancers in the LSS cohort (sex-averaged). The risk is shown for subjects at the attained age of 70 years after exposure at age 30.[22] The horizontal bars indicate 90% confidence intervals.

unless otherwise specified.

ERR/Gy of all solid cancers is 0.47, and it is therefore estimated that the cancer incidence among people exposed to 1 Gy is 47% higher than the incidence among unexposed people. As shown in the figure, cancer risks are increased significantly in most sites, such as the oral cavity, esophagus, stomach, colon, liver, lung, skin (non-melanoma), breast, ovary, bladder, central nervous system, and thyroid. The ERRs for pancreas, prostate, and renal cell cancers are not statistically significant.[22] These results suggest differences in radiation sensitivity by site, but the confidence intervals of all the sites overlap, and the differences in ERR by site cannot be verified statistically. Thus, care should be taken in interpretation. When comparing leukemia with all solid cancers in terms of the aforementioned ERR and estimated excess number of cases, the ERR/Gy is larger for leukemia, while the estimated excess number of cases is larger for solid cancers. This information indicates that solid cancers constitute a larger impact of radiation in the cohort than leukemia, despite the fact that leukemia is strongly associated with radiation, because leukemia is less common than solid cancers.

(3) Site-specific cancer risks

a. Stomach cancer

Until recently, stomach cancer had been the cancer with the highest incidence among Japanese people. It is the cancer with the highest confirmed numbers of mortality cases and incident cases in the LSS cohort. A significant increase in stomach cancer risk with radiation dose has been observed in both the mortality study (ERR/Gy = 0.33, 95% CI: 0.17, 0.52)[17] and the cancer incidence study (ERR/Gy = 0.34, 90% CI: 0.22, 0.47).[22] ERR in the cancer incidence study was higher in females (ERR/Gy = 0.47) than in males (ERR/Gy = 0.21), but there was no difference in EAR between males (9.4 cases per Gy per 10,000 person-years) and females (9.7 cases). It is therefore considered that the sex difference in ERR is caused by the higher background risk of stomach cancer in males compared with females.

In the study based on mail survey information,[23] analyses were conducted taking into account smoking and education. The relative risk (RR) was 1.71 (95% CI: 1.27, 2.30) among the subgroup exposed to ≥1 Gy, and the RR increased significantly with increasing radiation dose.

Another study looked at the association between radiation and 200 stomach cancer cases (separated into intestinal type and diffuse type). These cases were identified among 4,690 people who satisfied certain conditions such as participation in the AHS health examinations during the period 1981–2002, with their blood samples stored, and who had no cancer diagnosis prior to blood collection.[24] While radiation was significantly associated with diffuse-type stomach cancer (ERR/Gy = 0.33, 95% CI: 0.03, 0.83), no association was observed with intestinal-type stomach cancer (ERR/Gy = –0.06, 95% CI: –0.19, 0.21). By examining the immunosuppressive interleukin-10 (*IL-10*) genotype, significant association between radiation and diffuse-type stomach cancer was observed only for the homozygous, wild-type *IL-10* gene (ERR/Gy = 0.46, 95% CI: 0.02, 1.43), while the ERR due to radiation exposure for *IL-10* variant-type homozygotes was estimated to be around 0, showing no statistical significance. These findings indicate possible involvement of *IL-10* variants in the decrease of radiation risk for diffuse-type stomach cancer. The results suggest that *IL-10* gene polymorphisms play a role in individual differences in radiation-related, diffuse-type stomach cancer risk.

b. Colorectal cancer

Colon cancer is the third most common of the cancers in the LSS cohort in terms of number of cases.[22] A significant increase in colon cancer risk with radiation dose has been observed in both the mortality study (ERR/Gy = 0.34, 95% CI: 0.05, 0.74)[17] and the cancer incidence study (ERR/Gy = 0.54, 90% CI: 0.30, 0.81).[22] The ERR in the mortality study was about the same for males and females, but the risk ratio of females to males (F/M ratio) was 0.5 in the incidence study. It is not clear why a difference in F/M ratio exists between the mortality and incidence studies. Obesity is considered to be one of the risk factors for colon cancer. However, ERR/Gy for colon cancer estimated by an analysis allowing for body mass index (BMI) was 0.53 (95% CI: 0.25, 0.86), indicating that the extent of radiation effects did not change with BMI.[25] No significant association has been observed between radiation exposure and rectal cancer risks in either the mortality study (ERR/Gy = 0.17, 95% CI: <0, 0.64)[17] or the cancer incidence study (ERR/Gy = 0.19, 90% CI: <0, 0.47).[22]

c. Liver cancer

A significant increase in liver cancer risk with radiation dose has been observed in both the mortality study (ERR/Gy = 0.38, 95% CI: 0.11, 0.62) and the cancer incidence study (ERR/Gy = 0.30, 90% CI: 0.11, 0.55).[22] In a case-control study using stored tissue samples,[26] a strong multiplicative interaction between radiation exposure and hepatitis C virus

(HCV) infection was observed for the risk of hepatocellular carcinoma in subjects without cirrhosis. A nested case-control study using the stored serum of AHS subjects[27] and adjusting for alcohol intake, obesity, and smoking was also conducted. In that study's analysis, excluding those infected with hepatitis B or C virus, and taking other risk factors into consideration, the RR of non-B non-C hepatocellular carcinoma at a liver dose of 1 Gy was 2.74 (95% CI: 1.26, 7.04). This result indicates that radiation exposure confers an independent risk for hepatocellular carcinoma and may also multiply the risk associated with HCV infection in a subset of cases.

d. Lung cancer

A significant increase in lung cancer risk with radiation dose has been observed in both the mortality study (ERR/Gy = 0.75, 95% CI: 0.51, 1.03)[17] and the cancer incidence study (ERR/Gy = 0.81, 90% CI: 0.6, 1.1).[22] In the cancer incidence study,[22] the F/M ratio of ERR/Gy was relatively high, 4.8, but the F/M ratio was not statistically significant for EAR/Gy, making the high F/M ratio for ERR likely attributable to the much lower baseline rates of lung cancer among females than among males. Unlike the ERRs for many other sites, the ERR for lung cancer tended to increase with increasing age at exposure. This trend is assumed to be associated with the relationship between increased lung cancer incidence and increased smoking rate.

A study was conducted to assess the effects of radiation on lung cancer incidence after taking into account smoking, the most important risk factor for lung cancer,[28] based on information from smoking histories obtained in mail surveys for 1,803 lung cancer cases in the LSS cohort ascertained by histopathological review. The ERR/Gy due to radiation exposure among non-smokers (risk at age 70 after exposure at age 30) was estimated to be 0.59 (95% CI: 0.31, 1.0), and decreased with attained age with no departure from linearity. The ERR tended to increase with age at exposure, even after adjustment for smoking. The joint effect of smoking and radiation was super-multiplicative among light-to-moderate smokers, but the effect was additive or sub-additive for heavy smokers, for whom little radiation-related excess risk was observed (Figure 11). About 1/3 of the lung cancer cases in this population are explained as having been caused by smoking and 7% by radiation.

e. Breast cancer

A significant association between breast cancer risk and radiation exposure has been observed in both the mortality study (ERR/Gy = 0.90, 95% CI: 0.30, 1.78) and the cancer incidence study (ERR/Gy = 0.87, 90% CI: 0.55, 1.3).

It is also known that, among those exposed at an age of <20, breast cancer risk in those whose attained age is between 20 and 35 increases markedly, with ERR/Gy = 16.8 (Figure 12).[29] A case-control study interviewed 196 females in the LSS cohort diagnosed with breast cancer and 566 females without breast cancer, who were selected from the same cohort by matching on age at exposure, city, and estimated radiation dose. The study showed that the same risk-reduction factors for breast cancer confirmed among the general population (namely, first full-term pregnancy at younger age, prolificacy, and long lactation period) also reduced

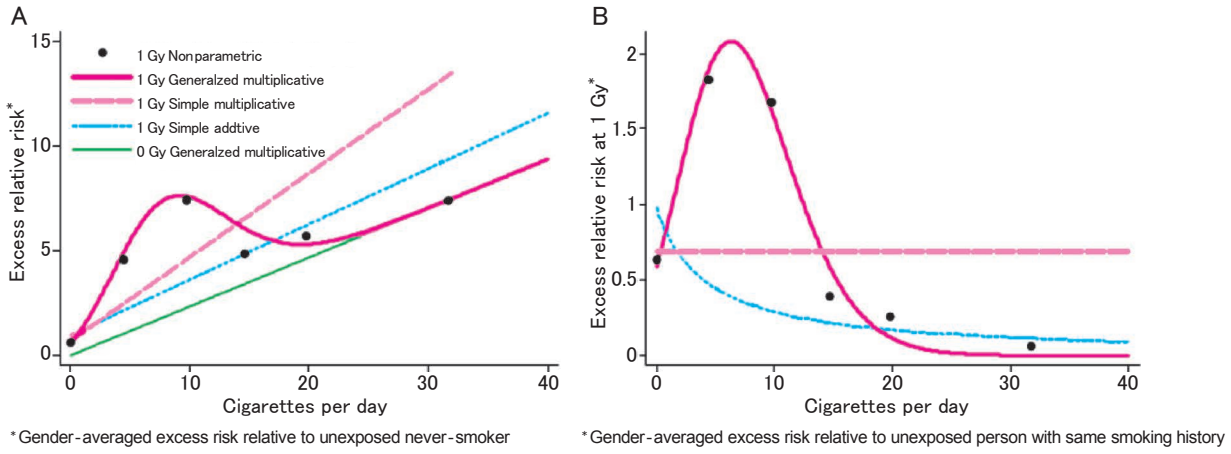


Figure 11. Change in ERR in relation to the number of cigarettes smoked per day.[28] The sex-averaged risk estimates at age 70 following radiation exposure at age 30, with smoking begun at age 20. Panel A describes ERR compared to a non-exposed non-smoker. Panel B indicates ERR for an exposure of 1 Gy compared to an unexposed person with the same smoking history.

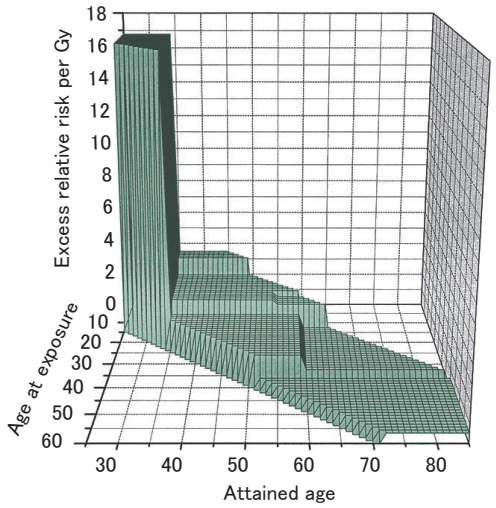


Figure 12. Bivariate isotonic regression: Breast cancer ERR/Gy with age at exposure and attained age as a monotonic/non-decreasing function[29]

breast cancer risk in those exposed to atomic bomb radiation.[30] Mammary gland tissue during the time between menarche and first childbirth is believed to be very sensitive to carcinogenesis. However, in a study involving the LSS cohort that compared radiation risk by time period (time between menarche and first childbirth, time before menarche, and time after first childbirth) no significant difference was seen.[31] In histopathological review of breast cancer cases, no difference in pathological findings has thus far been observed between exposed subjects and controls.[32]

f. Urinary organ cancer

A statistically significant increase in bladder cancer risk with radiation dose has been observed in both the mortality study (ERR/Gy = 1.19, 95% CI: 0.27, 2.65)[17] and the cancer incidence study (ERR/Gy = 1.23, 90% CI: 0.59, 2.1).[22] It is known that the variation in ERR of bladder cancer by age at exposure and attained age is smaller than that of other cancers. The ERR/Gy by sex in the cancer incidence study was 0.61 for males and 1.86 for females, with the risk for females about three times higher than that of males. Analysis has also been carried out to take into account the effects of smoking, fruit/vegetable intake, alcohol consumption, and education.[33] This analysis observed no major changes due to radiation based on consideration of these factors in terms of estimated ERR and F/M ratio.

No statistically significant increase in prostate cancer risk with radiation dose has been observed in either the mortality study (ERR/Gy = 0.33, 95% CI: <0, 1.25)[17] or the cancer incidence study (ERR/Gy = 0.11, 90% CI: –0.10, 0.54).[22] The reason why increased risk has not been detected is because prostate cancer is common among the elderly, although the number of patients identified through follow-up to date is still small, despite a recent rise in incidence in these populations.

g. Brain and central nervous system tumors

A significant association of brain and central nervous system tumor risks with radiation dose has been observed in the cancer incidence study (ERR/Gy = 0.62, 90% CI: 0.21, 1.2).[22] In a histopathological review of central nervous system tumors diagnosed during the period 1958–1995,[34] ERR/Gy of all central nervous system tumors was estimated to be 1.2 (95% CI: 0.6, 2.1). In this study, the risk was estimated at age 60 after exposure at age 30. By histological type, ERRs/Gy of meningioma, schwannoma, glioma, and pituitary tumors were 0.64 (95% CI: –0.01, 1.8), 4.5 (95% CI: 1.9, 9.2), 0.56 (95% CI: –0.2, 2.0), and 0.98 (95% CI: <–0.2, 3.5), respectively, showing a strong dose-response relationship for schwannoma.

h. Thyroid cancer

Thyroid cancer is not a very common cancer, but it has a relatively strong association with radiation. The association between thyroid cancer and radiation was demonstrated the earliest (10-plus years after exposure) of all the solid cancers observed among A-bomb survivors.[35] A significant increase in risk with radiation exposure was observed in the cancer incidence study (ERR/Gy = 0.57, 90% CI: 0.24, 1.1).[22] Furthermore, a recent study[36] analyzed 371 thyroid cancer cases confirmed by histopathological review from among 105,401 LSS subjects, and estimated ERR/Gy to be 1.28 (95% CI: 0.59, 2.70) and EAR per 100,000 person-years-Gy to be 29.5 (95% CI: 13.8, 49.6) (in both cases at age 60 after exposure at age 10). The radiation-associated thyroid cancer risk was higher among those exposed during early childhood, suggesting continuation of the risk throughout the lifetime, whereas no clear effects of exposure at age 20 or older were observed (Figure 13). Of the thyroid cancer cases developing among LSS subjects exposed to ≥5 mGy at the age of <20 years (113 cases), 36% were estimated to be attributable to radiation.

A prevalence study based on thyroid examination of AHS participants[37] found that thyroid cancer risk also increased with radiation dose, showing a linear dose-response relationship (excess odds ratio per Gy = 1.95, 95% CI: 0.67, 4.92). Further, an association between thyroid microcarcinoma (diameter of <1 cm) and radiation exposure has also been suggested.[38]

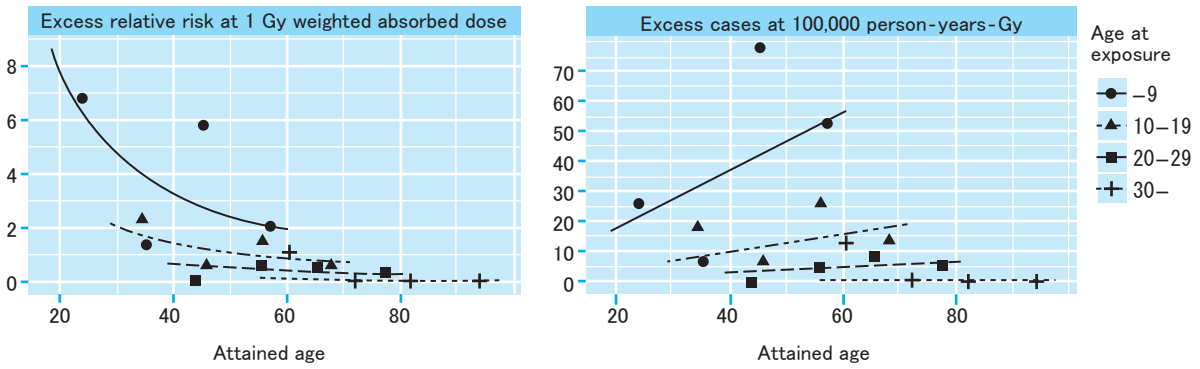


Figure 13. Fitted temporal patterns and variation with age at exposure in radiation-associated risk for thyroid cancer in the LSS cohort.[36] The left panel presents ERR at 1 Gy and the right panel shows the fitted excess absolute rate at 100,000 person-years-Gy. All curves and points represent sex-averaged estimates.

At RERF, characteristics of cancers induced by radiation exposure have been examined at the molecular level in a molecular oncological approach. It is thought that normal cells become cancerous due to the accumulation of various gene abnormalities. Generally, there are gene abnormality patterns unique to cancer tissue, and certain patterns (accumulation of characteristic abnormalities in particular genes) have been observed at high frequencies particularly in radiation-related thyroid cancer. For example, *RET* and *ALK* gene rearrangements are observed in papillary thyroid carcinoma in exposed adults. Papillary thyroid carcinoma with these abnormalities in gene rearrangements are frequently observed among survivors exposed to high doses during childhood.[39,40]

2. Noncancer diseases and abnormalities (excluding deaths due to blood diseases)

With regard to the effects of A-bomb radiation on noncancer diseases, recent analysis of LSS mortality data (1950–2003) shows a statistically significant increase with dose for death from diseases other than cancers (circulatory disease: ERR/Gy = 0.11, 95% CI: 0.05, 0.17; respiratory disease: ERR/Gy = 0.21, 95% CI: 0.10, 0.33).[17] Besides LSS mortality data, RERF has acquired much information about noncancer diseases through AHS health examinations and special tests. This information suggests that A-bomb radiation effects increased the risks of heart disease, stroke, thyroid benign tumor, hyperparathyroidism, hypertension, kidney disease, liver disease, uterine myomata, and cataract (Figure 14).

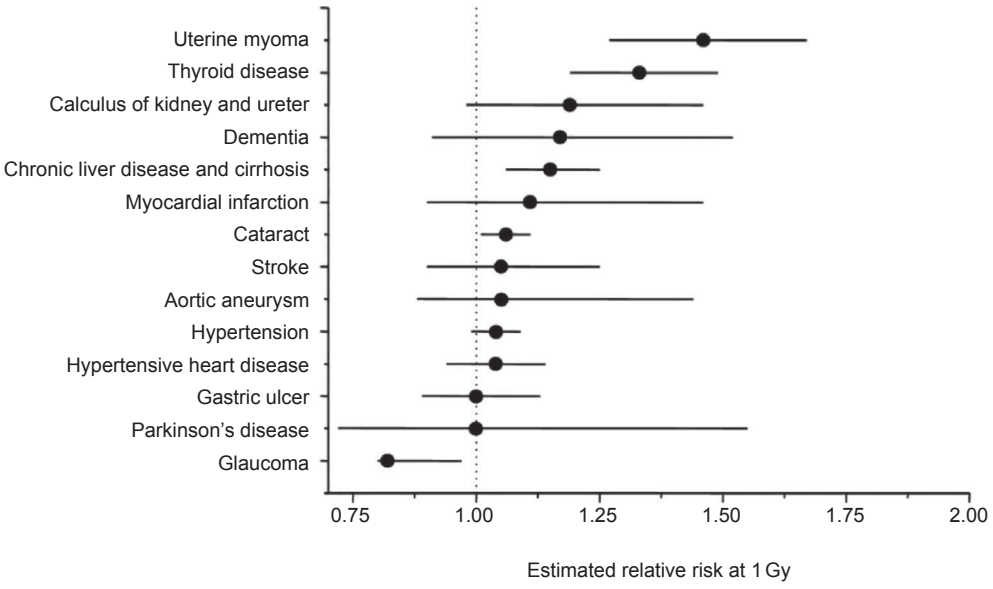


Figure 14. RR for noncancer diseases among AHS subjects exposed to 1 Gy of radiation (1958–1998).[18] The horizontal bars indicate the ranges of 95% confidence intervals.

There are several caveats to keep in mind when interpreting the results of the noncancer disease research. First, it is necessary to consider that the LSS mortality study examines only cause of death, and that AHS reports are based on studies conducted only of those who participate in health examinations. For example, of those who develop subarachnoid hemorrhage, which is a brain disorder, 50% die within a year of the episode.[41] On the one hand, AHS health examinations cannot detect those who died from subarachnoid hemorrhage between routine AHS health examinations and those who could not participate in the health examinations due to the long-term effects of subarachnoid hemorrhage. On the other hand, investigations of cause of death in the LSS might not be able to identify the other 50% who survived after the episode. Second, it is projected that rapid westernization of Japanese lifestyle as well as changes in medical technology may have modified the numbers of disease cases and complicated interpretation of the study results.

(1) Mortality and incidence of circulatory disease (heart disease and stroke)

Circulatory disease deaths account for a majority of worldwide death totals, and interpretation of the increased risk related to radiation exposure is an important issue.

Recent analysis of DS02-based LSS data (1950–2003) shows a significant association between circulatory disease mortality and A-bomb radiation exposure throughout the relevant period, with linear-quadratic and linear dose responses observed for stroke and heart disease, respectively (Figure 15). In addition, subtype-specific analyses suggest significant radiation effects on mortality due to hypertensive heart disease and heart failure.[42] Analysis of AHS data did not indicate such associations, but suggested the possibility of a quadratic dose response for myocardial infarction incidence among those exposed at ages <40 (RR/Gy = 1.25, 95% CI: 1.01, 1.36).[18] With regard to stroke, using DS02-based data we analyzed the period when prevailing diagnostic imaging techniques had improved accuracy in diagnoses for disease classification (1980–2003) and found a radiation-associated increase in risk for hemorrhagic stroke (including intracerebral hemorrhage and subarachnoid hemorrhage) but not for ischemic stroke (Table 8).[43] Detailed analysis will be necessary in the future taking into account the possibility of increased circulatory disease risks mediated by the known risk factors hypertension,[18] lipid metabolism abnormality,[44] and kidney disease.[45]

(2) Mortality and incidence of liver disease

With respect to liver diseases, RERF has thus far studied the prevalence of chronic liver disease (including chronic hepatitis, fatty liver, and liver cirrhosis) (refer back to Figure 14) and mortality from liver cirrhosis.

A report of analysis of all disease deaths other than tumor deaths in the LSS population indicated that mortality risk of liver cirrhosis tended to increase with radiation dose,[46–48] but pathological reviews taking into account HBV and HCV infection as well as alcohol consumption showed that radiation effects on liver cirrhosis were not significant.[49] A study based on autopsy diagnoses indicated that association between liver cirrhosis and radiation dose was significant or suggestive.[50–52]

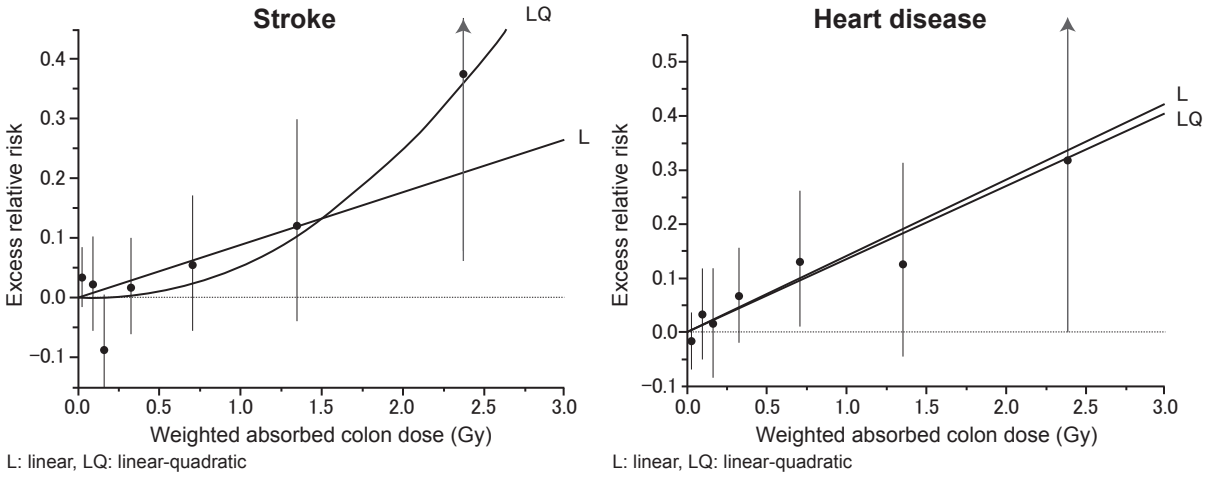


Figure 15. Dose response for circulatory disease mortality.[42] The vertical bars indicate the ranges of 95% confidence intervals.

Table 8. Age-adjusted stroke incidence[43]

Radiation exposure (Gy)	Sample size	Hemorrhagic stroke¶		Ischemic stroke	
		Events	Incidence*	Events	Incidence*
Men					
<0.05	1,539	33	12.2	112	40.5
0.05–1	1,266	37	17.6	81	38.5
1–2	376	13	21.4	20	34.9
≥2	130	5	25.2	8	46.3
p value†			0.006		0.788
Overall	3,311	88	15.7	221	39.4
Women					
<0.05	2,765	66	13.1	173	34.4
0.05–1	2,720	63	12.4	174	33.9
1–2	531	8	9.3	33	39.8
≥2	188	10	41.9	6	27.9
p value			0.098		0.930
Overall	6,204	147	13.1	386	34.4

¶ Hemorrhagic stroke includes intracerebral hemorrhage and subarachnoid hemorrhage.
* Incidence rate per 10,000 person-years
† Trend test

In the AHS population, a significant dose response was observed for chronic liver disease (including liver cirrhosis).[18,53] In consideration of the fact that the International Classification of Diseases (ICD) coding rules were revised in 1986, during the investigation period, and that introduction of abdominal ultrasonography brought about a pronounced increase in the number of chronic liver disease cases, however, we limited our work to the period from 1986 and thereafter and found that the RR for chronic liver disease was not significant (RR = 1.14 [95% CI: 0.84, 1.40]). Furthermore, when chronic liver diseases were classified into fatty liver and other types, a suggestive association with radiation dose was observed only for fatty liver risk (RR = 1.16 [95% CI: 0.99, 1.37]), indicating the possibility that the significance of the dose response observed for chronic liver disease arose from radiation-related fatty changes in the liver.

(3) Thyroid disease

Thyroid diseases are classified into benign or malignant nodular diseases and thyroid dysfunction with inappropriate hormone secretion. Thyroid nodules are observed at a high frequency in the general population, and when investigated by ultrasonography, such nodules are said to be detected on average in about 20% of the Japanese adult population.[54]

With regard to thyroid nodules, two cross-sectional studies were conducted as part of the AHS, one in the 1970s and the other in the 2000s. In a thyroid palpation study conducted during 1974–1976 among a population of those exposed at ages younger than 20 in Hiroshima and Nagasaki, analysis using T65D-based data suggested high frequencies of benign or malignant solitary thyroid nodules in a group exposed to over 100 rad (1 Gy). During 2000–2003, RERF conducted a large-scale cross-sectional study examining 4,091 people by ultrasonography (followed by cytologic diagnosis for nodules exceeding 1 cm in the long diameter). Analysis using DS02-based data revealed an association between the prevalence of benign thyroid nodules and thyroid radiation dose (excess odds ratio 1.53/Gy [95% CI: 0.76, 2.67]). Furthermore, since a negative association was found between age at exposure and ERR for benign thyroid nodules per Gy (p = 0.002), the possibility exists that benign thyroid nodules increased with decreasing age at exposure. No clear association with thyroid radiation dose was observed regarding thyroid dysfunction (hypothyroidism and hyperthyroidism).[37]

(4) Cataract

With ocular tissues, it is commonly understood that the lens is more sensitive to radiation than other tissues. One of the important late effects of radiation is lens opacity, or cataract. A short time after the A-bombings, an increase in cataract incidence among A-bomb survivors was reported,[55] and reports about A-bomb cataract were subsequently released by numerous researchers.[56–58] A-bomb cataract presents with a specific symptom (posterior subcapsular opacity), and it has been assumed that the detectable threshold values in A-bomb radiation exposure are 5 Gy for chronic radiation exposure over a prolonged

period of time and 0.5–2.0 Gy for acute radiation exposure.[59] In recent years, we performed slit-lamp microscopy on, and took digital images of, a portion of the AHS population, which suggested an increase in cataract other than the posterior subcapsular type. Since such issues as the quality of the images and the non-standardized nature of the diagnostic criteria have become apparent, however, further study of this particular issue is needed.

(5) Gynecological disease

The mail surveys conducted of LSS female subjects detected prematurity in natural menopause with increasing radiation dose (Figure 16).[60] The premature artificial menopause observed in this study can be explained by the increased incidence of A-bomb-radiation-induced uterine myoma (benign tumor of the uterus) found in the AHS (refer back to Figure 14).[18] Effects of radiation on ovarian function have been suggested, but studies of A-bomb survivors have not resulted in any evidence suggesting that radiation exposure may reduce fertility or chance of giving birth.

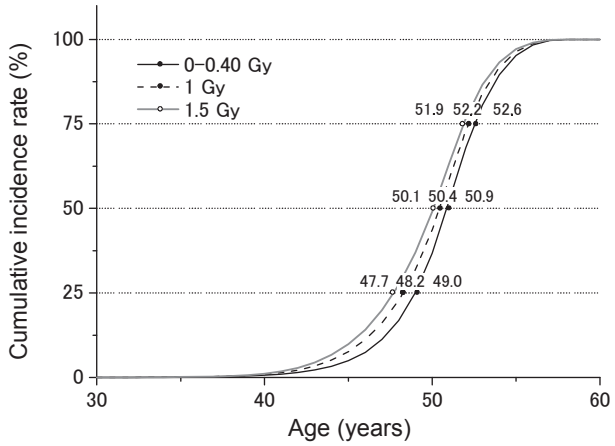


Figure 16. Cumulative incidence rate of natural menopause[60]

(6) Physical growth and development and bone and locomotor apparatus disease

Body measurements (height, weight, chest circumference, etc.) have long been carried out at ABCC-RERF to observe radiation effects on growth in A-bomb survivors exposed when young. Findings show that growth retardation is a general result of childhood exposure to high-dose A-bomb radiation. In the case of fetal exposure, no clear radiation effects were seen among those who were exposed to <1 Gy, but doses of ≥ 1 Gy did cause decreased adult height by about 6 cm (about 2.5 cm per Gy). Such an effect was already observed at age 10 among survivors exposed *in utero*. Since the gaps between individuals exposed as fetuses and unexposed people did not widen in subsequent years, however, it is believed that pubertal growth in height was not affected.[61] According to analysis of effects of childhood exposure at various ages, average height reductions per Gy of 2.0 cm in females and 1.2 cm in males were observed after exposure in infancy; the corresponding values were about 1.0 cm and 0.6 cm, respectively, after exposure at age 10.[62] It is generally known that in females early menarche is associated with growth in height, but no effects of radiation on age of menarche were observed.

As shown above, disorders in physical growth and development of A-bomb survivors who were exposed to radiation during the period of active bone growth prior to puberty have been reported, but no association between late-life skeletal abnormality (prevalence of osteoporosis and vertebral body fracture) and A-bomb radiation has been observed among A-bomb survivors.[63–65]

(7) Skin disease

Burns, external injuries, and dermatitis due to the thermal rays, fires, blasts, and acute radiodermatitis from the A-bombings were early skin disorders observed among A-bomb survivors. It was reported that harsh hygienic conditions at the time contributed to delayed healing of such conditions.[66] Furthermore, either hypertrophic cicatrix (scarring) or keloidal tissue (pinkish, elevated scar growth) was found in 50–70% of those with scars as a result of burns.[67,68] These hyperplastic scar tissue skin manifestations afflicting A-bomb survivors, which became apparent 3–4 months after the A-bombings, peaked 2–3 years after the bombings, and then declined with time.

ABCC conducted clinical dermatological evaluation of 10,650 AHS subjects during 1964–1966.[69] Findings indicated that A-bomb survivors exhibited a higher frequency of atrophic scars, pigmentation, and depigmentation, and showed a tendency for fine telangiectasia (small dilated blood vessels) of the arm that increased with increasing radiation dose. The relationship between skin changes due to aging and radiation exposure was also examined, but it was found that any association was limited to increases in poliosis (white hair) and facial senile elastosis (loss of elasticity of the skin due to the degeneration of elastic fiber that helps maintain skin turgor).

(8) Psychoneurological and psychological effects

The A-bombings of Hiroshima and Nagasaki were

unprecedented disasters never before experienced by humankind. In addition to physical symptoms, it is believed that the loss of or changes in human, social, and physical environments brought about psychoneurological and psychological effects, causing post-traumatic stress disorder (PTSD) and other disturbances among A-bomb survivors. Such psychoneurological and psychological effects may persist in negatively affecting the health of survivors over the long term. Nevertheless, there are limited numbers of studies and reports on psychoneurological and psychological effects caused by the A-bombings.

With regard to presence and/or absence of physical symptoms, a self-administered questionnaire-based survey was conducted of the AHS population during the period 1962–1965. Analysis of the survey results in terms of acute radiation symptoms and distance from the hypocenter revealed the highest frequency of complaints of various physical symptoms, fatigability, and emotional disturbances such as fear and anxiety in the group of proximally exposed survivors who had developed acute radiation symptoms.[70,71]

LSS analysis related to suicide conducted during 1950–1966, however, yielded no evidence of a high suicide rate among A-bomb survivors.[72]

3. Abnormality in the immune system and inflammation

Immune system alterations observed in A-bomb survivors mainly comprise attenuation of T-cell-dependent adaptive immunity and a state of low-grade inflammation. Low-grade inflammation is thought to be caused by activation of innate immunity. Many related issues remain unresolved, including the mechanisms behind alterations in the immune system due to radiation exposure and how such immune changes affect the onset of disease. However, most radiation-related alterations in the immune system resemble age-related attenuation of immune function (immunosenescence) (Figure 17). For example, aging decreases production of T lymphocytes, leading to a decrease in the number of naïve T lymphocytes (immature T lymphocytes that have never been activated) in blood but an increase in production of memory T lymphocytes (that have been activated) with weakened functions and decreased diversity in antigen recognition. Meanwhile, the possibility of dose-dependent reductions in the naïve T-lymphocyte pool and memory T-lymphocyte functions of A-bomb survivors have been reported.[73–75] Furthermore, generally speaking, the production of inflammatory proteins and cytokines by innate immune cells and the acceleration of inflammation increase with aging. RERF has obtained research results showing high levels of these inflammatory proteins and cytokines also among people exposed to high radiation doses.[76] These results suggest that A-bomb radiation might have accelerated immunosenescence.[77–79]

【B】 Results from studies of *in utero* survivors

1. Intellectual impairment

Various findings from epidemiological and experimental studies have indicated that development of the embryo and fetus is adversely affected by radiation exposure. Epidemiological data on persons exposed to radiation *in utero* suggest the possibility of adverse effects on brain development at certain gestational ages. More specifically, high radiation exposures *in utero* at 8–15 weeks after conception, a time during which the cerebral cortex is developing, led to severe intellectual impairment, decreased academic performance and intelligence quotient (IQ) scores,

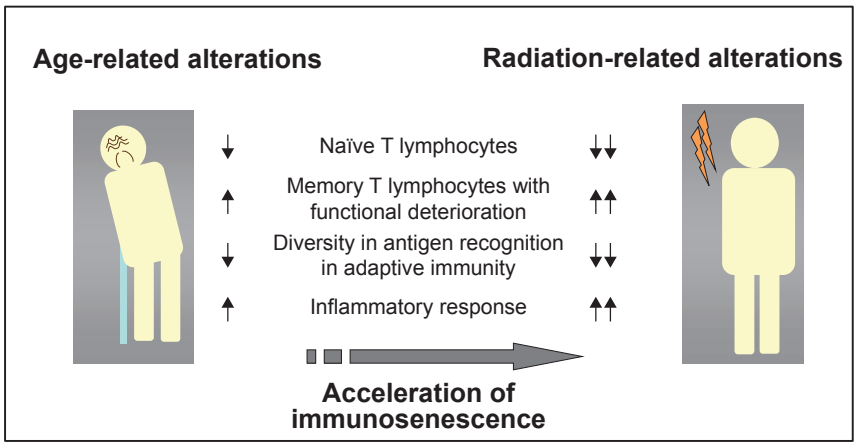


Figure 17. Acceleration of immunosenescence due to radiation exposure

and increased epileptic seizures. Decreased academic performance and IQ scores as well as excess cases of intellectual impairment were also observed among those exposed *in utero* at 16–25 weeks after conception (Figures 18 and 19). DS86-based assessment suggests the possibility of a threshold for severe intellectual impairment when exposure takes place *in utero* at 8–25 weeks after conception. There has been no evidence to indicate effects on brain disorders from *in utero* exposure among individuals exposed at less than 8 weeks or at 26 weeks or later after conception.[80]

Five survivors with intellectual impairment exposed *in utero* at 8–15 weeks after conception underwent magnetic resonance imaging (MRI) of the brain. Of these five survivors, two exposed *in utero* at 8–9 weeks after conception were found to have a large region of ectopic gray matter. This finding may indicate erroneous nerve cell migration to the function site during cerebral development. Therefore, exposure *in utero* at such gestational ages is suggested to give rise to structural abnormalities in the brain.[81]

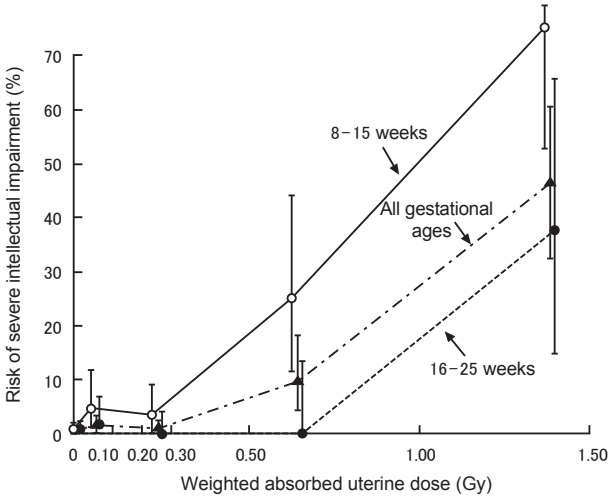


Figure 18. Severe intellectual impairment as related to radiation dose and gestational age among A-bomb survivors exposed *in utero*.[81] The vertical bars indicate 90% confidence intervals.

2. Growth impairment

Effects from *in utero* radiation exposure have been studied and reported as growth indices in terms of physical measurements such as head circumference, seated height, and standing height. Small head circumference suggests underdevelopment of the cranium and possibly of the brain. To study the correlation between intellectual impairment and small head circumference observed among *in utero* survivors, head circumference of these survivors was measured. Of the 1,473 *in utero* survivors whose head circumference was measured at ages 9–19, 62 were found to have a small head circumference (i.e., more than two standard deviations [SD] smaller than the cohort average by sex and age at the time of measurement). Radiation effects on the frequency of small head circumference were observed at 0–15 weeks after conception. No apparent radiation effects on the frequency of small head circumference, however, were observed at 16 weeks or later after conception. Since a small head circumference does not necessarily equate to intellectual impairment, an embryologic difference between the development of small head circumference and intellectual impairment is suggested.[82]

As for other physical measurements, annual body

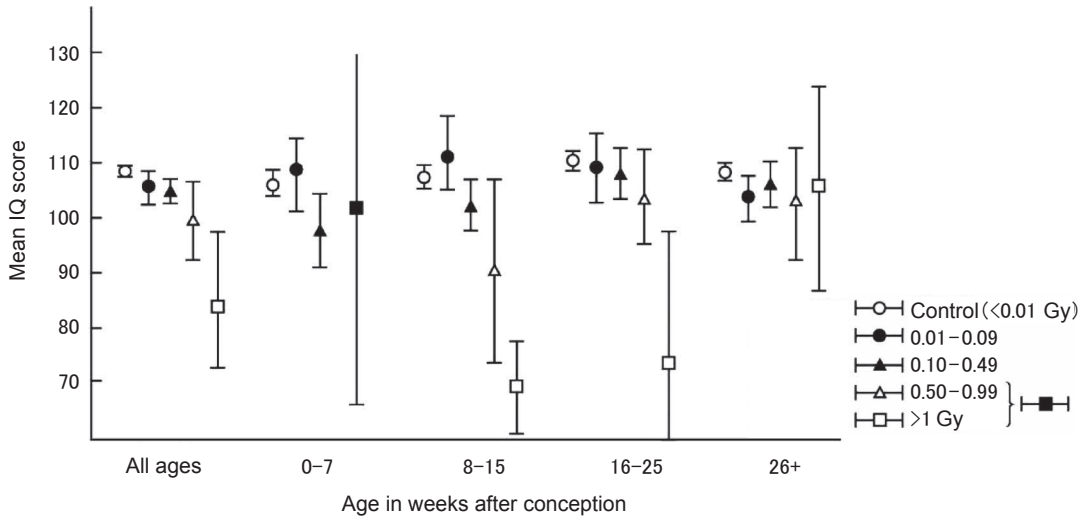


Figure 19. Mean IQ scores as related to uterine radiation dose (DS86) and gestational age among A-bomb survivors exposed *in utero*.[81] The vertical bars indicate 95% confidence intervals.

measurements of survivors exposed *in utero* have also demonstrated an overall reduction in adult height and weight (at age 18) as well as seated height and chest circumference among *in utero* survivors with small head circumference.[83]

3. Malignant tumors

The cancer incidence study[84] conducted during 1958–1999 (attained age: 12–55 years) indicated a significant increase in cancer risk among *in utero* survivors as adults (sex-averaged ERR/Gy = 0.42 at attained age of 50, 95% CI: 0.0, 2.0), which is less than that for survivors exposed as children (ERR/Gy = 1.7, 95% CI: 1.1, 2.5). When EAR from both groups was compared, EAR increased significantly with attained age for survivors exposed as children, while EAR for *in utero* survivors remained nearly unchanged. EAR per Gy per 10,000 person-years = 6.8 (95% CI: 0.002, 48) at attained age of 50 for *in utero* survivors is significantly lower than EAR per Gy per 10,000 person-years = 56 (95% CI: 36, 79) for survivors exposed as children. It had been supposed that the younger the child was at the time of the bombings, the higher the risk of radiation-induced cancer, and that such a risk would be even higher for *in utero* survivors. However, the study results obtained thus far suggest that the lifetime risk of solid cancers among *in utero* survivors may be lower than that of survivors exposed as children (Figure 20).[84]

Nevertheless, *in utero* survivors have just recently entered their cancer-prone ages, and the numbers of cancer cases and deaths ascertained to date account for less than half of the predicted lifetime risk. Conduct of a continuation of follow-up is therefore necessary to clearly define *in utero* cancer risk.

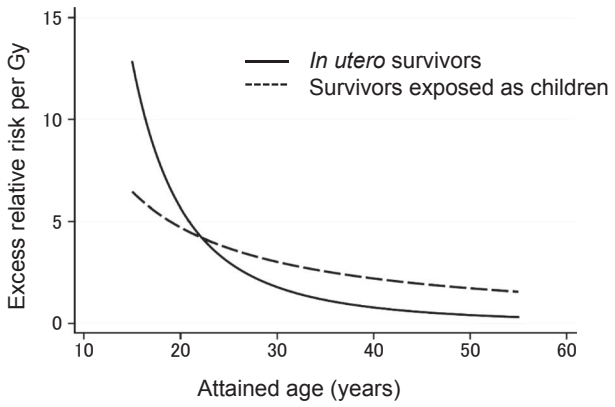


Figure 20. Change in ERR/Gy for solid cancer incidence of *in utero* survivors and those exposed as children in relation to attained age[84]

4. Noncancer diseases during adulthood

A study of *in utero* survivors with a focus on noncancer diseases that occurred during adulthood up to the age of 60 provided no evidence of radiation effects on the prevalence of thyroid diseases or cataracts nor on the development of hypertension, hypercholesterolemia, or cardiovascular diseases (cerebral infarction and myocardial infarction).[85] Considering that the subjects were relatively young at the time of the study, the incidences of these diseases and conditions could well increase in the future, making it important to continue the follow-up study of *in utero* survivors.

【C】 Results from studies of children of A-bomb survivors (genetic effects)

1. Birth defects (stillbirth, malformation, and neonatal death)

During the period 1948–1954, ABCC conducted a large-scale neonatal study to investigate the possibility of germ cells being affected by A-bomb radiation that might result in an increase in birth defects among the children of A-bomb survivors.[86]

In the study, more than 77,000 newborns during the first two weeks after birth were examined by physicians in Hiroshima and Nagasaki. Table 9 shows percentages of malformations diagnosed in these examinations.[86] Of the 65,431 newborns who met such conditions as no blood relationship between parents, 594 (0.91%) had malformations, but no association with parental radiation exposure was found. Malformations seen during the examination of the newborns included anencephaly, cleft palate, club foot, cleft lip with or without cleft palate, polydactyly, and syndactyly. These malformations were commonly seen in other populations, and the frequency of 0.91% was close to the result (456/49,654 = 0.92%) obtained from a general population studied by the Tokyo Red Cross Hospital during 1922–1940. Other birth defects (stillbirth, neonatal death, death within nine months after birth) also showed no association with parental radiation exposure. Reanalysis conducted subsequently using DS86 estimated doses showed the same results (Table 10).[87] Some of the newborns were examined again at ages 8–10 months. Again, there was no evidence of association between malformation frequency and parental radiation dose.[86]

2. Sex ratio

In the past, lethal mutations of the X chromosome in sperm and eggs caused by radiation exposure were thought to give rise to a disproportionate birth sex

Table 9. Malformation frequency in relation to parental exposure conditions[86]

Mother's exposure condition	Father's exposure condition		
	Not in cities	Low-to-moderate doses	High doses
Not in cities	294/31,904 (0.92%)	40/4,509 (0.89%)	6/534 (1.1%)
Low-to-moderate doses	144/17,616 (0.82%)	79/7,970 (0.99%)	5/614 (0.81%)
High doses	19/ 1,676 (1.1%)	6/ 463 (1.3%)	1/145 (0.7%)

Table 10. Birth defects (malformations, stillbirths, and neonatal deaths within two weeks of birth) among children of A-bomb survivors[87]

Mother's weighted absorbed dose (Gy)*	Father's weighted absorbed dose (Gy)*		
	<0.01	0.01–0.49	≥0.50
<0.01	2,257/45,234 (5.0%)	81/1,614 (5.0%)	29/506 (5.7%)
0.01–0.49	260/ 5,445 (4.8%)	54/1,171 (4.6%)	6/133 (4.5%)
≥0.50	63/ 1,039 (6.1%)	3/ 73 (4.1%)	7/ 88 (8.0%)

* DS86 estimated dose, neutron RBE = 20

ratio. This idea prompted a sex-ratio study of the children of A-bomb survivors.[86] An early study (1948–1953) suggested that there was a decrease in sex ratio (number of male babies per 100 female babies) from 104.1 to 101.4 with increasing radiation dose when mothers were exposed to A-bomb radiation and an increase from 104.1 to 106.4 when fathers were exposed. These results, however, were not statistically significant. Data collection continued through 1962. Information ultimately obtained from a total of more than 140,000 births showed no significant association between parental radiation exposure and the birth sex ratio of their children.

3. Chromosome aberrations

Extensive chromosome analyses have been carried out in the children of A-bomb survivors (F1 offspring) to determine whether stable aberrations were induced by radiation in parental germ cells (reciprocal translocations and inversions). No evidence has been found to suggest increased aberrations in this F_1 population.

Studies compared 8,322 persons having one or both parents within 2,000 meters of the A-bomb hypocenters (estimated doses ≥0.01 Gy) and 7,976 persons with both parents beyond 2,500 meters (estimated doses <0.01 Gy) or not in the cities at the time of the bombings. Eighteen persons in the exposed group and 25 controls carried stable aberrations (Table 11). Subsequent tests of parents and siblings showed that most aberrations were pre-existing and inherited from one of the parents. Only one individual from each group had a newly arisen aberration. The origin of aberrations in 16 cases could not be determined because the parents had either died or did not wish to participate in the study. Dose distributions, however, were similar in tested and untested parents, and therefore refusal to participate in the study did not likely cause a bias in the result.

4. Genetic effects studies at the protein level and subsequent DNA studies

(1) Blood protein mutations (1975–1985)

In 1976, when technologies for direct screening of DNA mutations were not yet available, RERF used two kinds of protein alterations as potential markers of mutation. One was a rare electrophoretic variant arising from base substitution mutations and was detected by one-dimensional electrophoresis. The other was an enzyme-deficient protein variant caused by deletion mutations.

Table 11. Stable chromosome aberrations in children of A-bomb survivors[88]

	Controls (7,976 children)	Exposed (8,322 children)
Total number of children with stable aberrations	25 (0.31%)	18 (0.22%)
Inherited from either parent	15 (0.19%)	10 (0.12%)
Newly arisen	1 (0.01%)	1 (0.01%)
Parental origin untested	9 (0.11%)	7 (0.08%)

Over the course of 10 years, a total of about 24,000 children of LSS survivors or controls were screened in an electrophoretic study of variants of 30 blood proteins (Table 12); approximately 10,000 of these children were also tested for mutations with decreased enzyme activity (Table 13). The children were classified into two groups according to the combined parental gonadal dose for each child: ≥0.01 Gy (exposed group) or <0.01 Gy (control group). The results indicated that only five electrophoretic variants (two in the exposed group and three in the control group) and one enzyme-deficient variant (in the exposed group) originated from new mutations in parental germ cells.

These protein-level studies did not show a significant difference in mutation rates between the exposed and control groups, meaning that they were unable to establish the presence of genetic effects from radiation.

(2) DNA studies (1985–present)

For DNA studies of 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 doses as high as 0.01 Gy, biological samples were collected. DNA was extracted from cell lines established from peripheral blood B lymphocytes. Uncultured lymphocytes and polymorphonuclear leukocytes were also preserved in anticipation of improved methods through advances in DNA analysis techniques in the future. Pilot studies have been conducted using DNA from 100 families, 50 having only one parent exposed to high doses (≥0.5 Gy) 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.

STRs, common throughout the human genome, are highly repetitive short sequences of DNA. STRs often indicate polymorphisms with different repeated numbers. Of those, genetically unstable and highly polymorphic STRs with a high background mutation rate are known as microsatellites with repeated sequences of 1–5 base pairs and minisatellites with repeated sequences of 6–100 base pairs. Through these STRs, researchers believed that radiation effects might be observable with a relatively small number of subjects. Eight highly polymorphic human minisatellite loci were studied in 61 children with exposed parents (mean dose: 1.47 Gy), and 58 children of the control group and their parents. The mutation rates were 2.6% for the exposed group and 2.8% for the control group, indicating no genetic effects (Table 14).[92] Microsatellite loci also have a high background mutation rate. A study looking at 40 microsatellite loci among 66 children of an exposed group (mean dose: 1.56 Gy) and 63 children of a control group and their parents showed mutation rates of 0.39% and 0.35% for the exposed and control groups, respectively, but the difference was not significant. The study thus indicated no genetic effects from parental exposure to radiation.[93]

Most genome mutations caused by ionizing radiation are believed to be deletion mutations. Screening of deletions was conducted using an improved DNA two-dimensional electrophoresis system for analyses of whole genome DNA.[94] Using this method, DNA

Table 12. Results of protein electrophoretic study[89–91]

	Controls (<0.01 Gy)	Exposed* (≥0.01 Gy)
Number of children examined	12,297	11,364
Loci tested	589,506	544,779
New mutations	3	2
Mutation rate/locus/generation	0.5×10^{-5}	0.4×10^{-5}

* Mean parental gonadal dose = 0.49 Gy (DS86), neutron RBE = 20

Table 13. Results of screening for mutations with decreased enzyme activity[90]

	Controls (<0.01 Gy)	Exposed (≥0.01 Gy)
Number of children examined	5,026	4,989
Loci tested	61,741	60,529
New mutations	0	1
Mutation rate/locus/generation	0	2×10^{-5}

Table 14. Mutations at eight STR (minisatellite) loci[92]

	Controls (<0.01 Gy)	Exposed* (≥0.01 Gy)
Number of children examined	58	61
Minisatellite loci tested	1,403	496
Mutations detected	39	13
Mutation rate/loci/generation	2.8%	2.6%

* Mean parental gonadal dose = 1.47 Gy (DS86), neutron RBE = 10

fragments produced with the restriction enzyme *Not*I are electrophoresed, and approximately 2,000 DNA fragments can be potentially analyzed in one run to search for deletion mutations. Upon analysis of 62 children from 50 control families, and 66 children from 50 exposed families (mean dose: 1.7 Gy) and their parents, one deletion mutation was detected among 56,176 loci from the control group, but no mutations were detected among 59,942 loci from the exposed group.

In early 2000, a study was initiated to detect changes in copy number variations (CNVs) using the microarray-based comparative genome hybridization (CGH) method. A pilot study was conducted to investigate 40 children each from the exposed and control groups, using microarrays containing about 2,500 human genomic DNA clones (termed PAC or BAC) selected as probes at intervals of approximately 1,200 kb. The array CGH method was performed, resulting in a total of 251 CNVs being detected. However, they were not *de novo* mutations, as it was later confirmed that all of these CNVs were pre-existing and inherited from one of the parents.[95]

Studies are ongoing using high-density microarrays that can detect small-to-large mutations in the entire genome at an individual genomic level. We are also exploring the possibility of risk assessment based on whole genome sequencing. Researchers expect that more detailed, genome-wide findings pertaining to genetic effects from radiation will be obtained in the near future.

5. Epidemiological and clinical studies

No effects from parental radiation exposure have thus far been observed in mortality studies of A-bomb survivors' children (second-generation A-bomb survivors), as measured at birth and in childhood,[96] under the age of 20,[97] and at 20 years of age or older (average age: 46).[98] Long-term follow-up studies will be necessary, however, since the cumulative mortality of those in the latest study, conducted on the cohort consisting of participants aged 56 years or younger, was only 3.5%.

Studies of childhood leukemia and early-onset solid cancers among the original follow-up cohort have shown no effects from parental radiation exposure on the onset of either condition among those younger than age 20[99] or between ages 20–40.

The latest cancer incidence study[100] does not clearly indicate effects of parental radiation exposure on the children's cancer incidence. Incidences of leukemia and lymphoma up to the age of 20 among A-bomb survivors' children whose paternal radiation dose was 5–49 mGy did not show any significant difference compared to those whose paternal radiation dose was <5 mGy (RR = 1.07, 95% CI: 0.36, 3.13). Nor was a significant difference observed in A-bomb survivors' children whose maternal radiation dose was 5–49 mGy as compared to those with maternal dose <5 mGy (RR = 1.55, 95% CI: 0.59, 4.28). There were no leukemia or lymphoma cases diagnosed among the A-bomb survivors' children younger than age 20 whose paternal and/or maternal radiation dose was ≥50 mGy. Among the A-bomb survivors' children aged 20–40, no significant difference in leukemia or lymphoma incidence has been observed for those whose paternal radiation dose was 5–49 mGy, 50–149 mGy, 150–499 mGy, or at least 500 mGy, as compared to those whose paternal dose was <5 mGy (Figure 21). Moreover, no significant difference has been observed for maternal radiation dose. The same comparison was made for solid cancer incidence for those less than age 20 as well as those aged 20–39, and no significant difference was observed for either age group. However, considering that the cohort is just at the beginning of the age range during which adult-onset cancers (mainly solid cancers) commonly occur, it is still premature to reach any conclusions, and therefore further studies should be conducted.

6. Prevalence of lifestyle diseases

The Clinical Health Study of the Children of A-bomb Survivors (cross-sectional study) conducted during 2002–2006 by RERF is the first epidemiological study to look at the genetic effects of radiation on adult-onset lifestyle diseases (excluding cancers). In

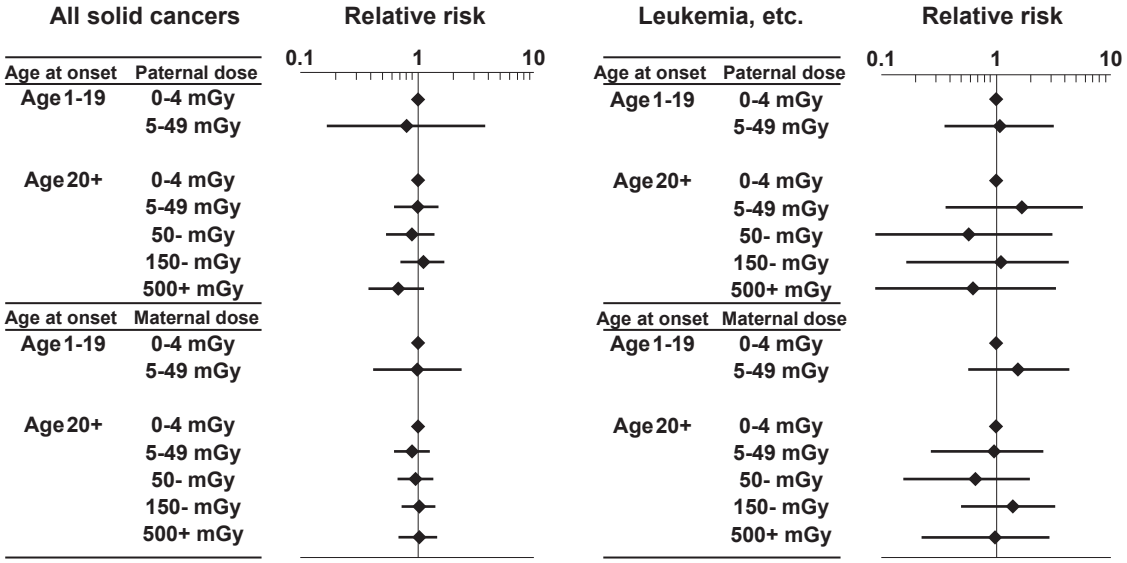


Figure 21. Parental radiation dose and risk of cancer incidence in A-bomb survivors' children born during 1946–1984 (follow-up period: 1958–1997).[100] The horizontal bars indicate 95% confidence intervals.

this study, we investigated the association between prevalence of adult-onset multifactorial diseases and parental radiation exposure in 11,951 A-bomb survivors' children in Hiroshima and Nagasaki. Thus far, however, no association has been observed between parental radiation exposure and adult-onset multifactorial diseases collectively among these children.[101] Moreover, no evidence has been observed showing an association with increase in the prevalence of any one of the multifactorial diseases separately.[102] Multifactorial disease is a generic term for diseases commonly seen in adulthood, the onset of which is typically associated with lifestyle factors, and is defined by either the history or presence of hypertension, diabetes, hypercholesterolemia, myocardial infarction, angina, or stroke. The mean age of the cross-sectional study participants was 48.6 years, and 54% were in their 50s. The prevalences of multifactorial diseases at the time of health examination were 59.8% and 49.9% for men and women, respectively, with hypercholesterolemia and hypertension the most commonly observed conditions.

We analyzed the association of prevalence of multifactorial diseases with both paternal and maternal radiation doses, after adjusting for factors such as age at the time of health examination of A-bomb survivors' children, city, sex, BMI, smoking and drinking habits, occupational category, menopause, and paternal and maternal history of multifactorial diseases. The odds ratios of the prevalence of multifactorial diseases among the children of A-bomb survivors were 0.91 (95% CI: 0.81, 1.01, p = 0.076) and 0.98 (95% CI: 0.86, 1.10, p = 0.71) for paternal and maternal doses per Gy, respectively, with neither showing significant dose-response relationships (Table 15).[101] The analysis results by sex suggested a negative association between paternal dose and the prevalence of multifactorial diseases for men (odds ratio: 0.76, 95% CI: 0.65, 0.89). No statistically significant relationship was observed between maternal dose and the prevalence of multifactorial diseases for men or between parental doses and the prevalence of multifactorial diseases for women (Table 15). In addition, no evidence was found of a radiation risk in children depending on parental age at the time of exposure, time elapsed between exposure and birth, or parental multifactorial disease history. The analysis results by sex suggested only a negative association between the prevalence of multifactorial diseases and paternal dose for male children of A-bomb survivors.

Caution is required in interpreting these results, however, since it is not an easy task to judge whether they are significant from a biological standpoint or simply the result of a self-selection bias, which is caused by differences in participation in the health examinations affected by such conditions as health status and parental radiation exposure. A review of self-selection bias was important considering that among the study subjects contacted only about half participated in the health examinations. In our review of self-selection bias, no association was observed between cancer history and parental doses for male study participants. However, in terms of self-selection bias, we observed a positive association between can-

cer history and maternal dose for female participants. We then compared the participation rate of those who self-reported disease(s) in the mail survey (including both the participants and non-participants of health examinations) with parental doses and found that the participation rate was high among people who self-reported hyperlipidemia and whose mother's dose was >0 Gy, but no association was observed between maternal dose and the participation rate of those with multifactorial diseases other than hyperlipidemia. No association was observed between paternal dose and the participation rate of the study subjects with any of the multifactorial diseases. From such results, no effects of self-selection bias on the analysis results were observed.

In summary, we cannot say at the present time that there is evidence of an increase in multifactorial disease risks for the children of A-bomb survivors associated with parental radiation exposure. Considering that history and incidence of multifactorial diseases typically increase with age, continuation of the investigation of genetic effects of radiation is crucial. RERF initiated a study on the incidence of such multifactorial diseases due to parental radiation exposure starting in 2010 as the Longitudinal Clinical Study of the F_1 Offspring of A-bomb Survivors.

Table 15. Association between parental radiation dose and prevalence of multifactorial diseases* among A-bomb survivors' children (odds ratio)[101]

	Odds ratio per Gy and 95% confidence interval		
	All participants	Male	Female
Paternal dose	0.91	0.76	1.04
	0.81–1.01	0.65–0.89	0.90–1.21
Maternal dose	0.98	0.97	0.98
	0.86–1.10	0.81–1.17	0.83–1.16

* Multifactorial disease is defined as having a history of, or being affected by, at least one of the following diseases/conditions: hypertension, diabetes, hypercholesterolemia, myocardial infarction, angina pectoris, and stroke. Multifactorial disease is a generic term for a group of diseases that generally develop during adulthood in association with lifestyle.

【6】 Future research themes

RERF studies are expected to achieve new potential through the use of valuable biosamples from A-bomb survivors to understand the risks revealed during the course of our epidemiological research. Our future research activities are projected to focus on more accurate risk assessment for the diseases that have increased due to radiation exposure, and biological verification of the mechanisms behind the onset of these diseases.

1. Radiation risk among A-bomb survivors and mechanistic elucidation

RERF scientists are expected to actively conduct research to review risk models for radiation exposure and elucidate effects of risk modifiers such as age at the time of bombing, time elapsed since exposure, age at onset, environmental factors including lifestyle, and genetic susceptibility. In cases of childhood/fetal exposure to radiation, age at the time of bombing is an especially important factor.

Researchers in fields such as radiation protection and radiobiology are interested in how radiation affects disease onset and what the mechanisms are involving factors related to such disease.

(1) Progress in research integrating molecular epidemiology with clinical/pathological information

Our ultimate goal is to identify molecular oncological characteristics that allow distinctions to be made between cancers attributable to radiation exposure and those due to other causes. New analytic techniques are required for achieving this goal. To this end, we are currently working to analyze genes and proteins in cancer tissue samples from A-bomb survivors, establishing methods that take into account clinical and pathological information, and clarifying characteristics of radiation-related cancers at the molecular level.

(2) Research on genetic susceptibility to radiation-related disease and epigenetic alterations

It has been theorized that individual differences exist in terms of sensitivity to radiation-induced disease and that these differences are partly attributable to subtle differences in the structures of individual genomes. Researchers around the world are intent on studying the association between onset of various kinds of disease and genomic structure with the aim of disease prevention and drug development. RERF genomic research aims specifically at elucidation of mechanisms behind the onset of radiation-related diseases. Epigenetic alterations (i.e., changes in the genomic structure without DNA base sequence changes), which are also affected by aging and environmental factors, are thought to sometimes serve as causes of multiple diseases including cancer. RERF is currently investigating the possibility that previous radiation exposure might affect epigenetic alterations, leading to an increase in disease risks.

(3) Research on cardiovascular disease (CVD)

The results of various studies of A-bomb survivors suggest correlations between radiation and increased risks for hypertensive cardiovascular disease and cerebral stroke, as well as hypertension, a condition that plays a role in the pathogenesis of these diseases. On the other hand, studies of low-dose radiation exposure, including occupational radiation exposure among nuclear facility workers and environmental low-dose radiation exposure, have shown inconsistent results. Researchers in the fields of radiation protection, radiobiology, and cardiology are exhibiting interest in this issue. RERF has consequently established a cardiovascular disease research project, coordinating multidisciplinary investigations to determine whether the risk of cardiovascular lesions truly increases with increasing radiation dose. As part of this work, we are using model animals that have been irradiated at precise levels to examine these events and elucidate the mechanisms behind any such increased risk.

2. Review of uncertainty in radiation dose estimates

In the case of A-bomb survivors exposed in concrete buildings or bomb shelters or under complicated shielding conditions (e.g., Nagasaki factory workers), it was impossible not only to generalize shielding conditions but also to calculate individual doses, resulting in about 7,000 “dose unknown” cases in the LSS population. From among these cases, it is necessary to review the possibility of making dose calculations for at least 2,000 concrete building shielding cases and 1,600 bomb shelter shielding cases, as well as the Nagasaki factory shielding cases. We have completed organ dose calculations for 15 organs, but it also will be necessary to calculate organ doses for the heart and other vital organs in the future. We will also further consider the refinement of dose calculations for childhood radiation exposure.

3. Review of genetic effects in children of A-bomb survivors

With regard to adult-onset diseases among children

of A-bomb survivors that are attributable to parental radiation exposure, we are continuing the conduct of our epidemiological research project, and follow-up will require several decades to establish definitive results.

Recent developments in genome analysis techniques are expected to contribute to better detection of the genetic effects of A-bomb radiation. It is also expected that use of model animals and analysis using whole-genome DNA sequencing technology will enable more comprehensive and accurate assays of the frequency of molecular genetic effects of radiation exposure in the children of A-bomb survivors.

【7】 Utilization of RERF study results by international organizations

The findings obtained from studies of the long-term health effects of A-bomb radiation conducted at ABCC-RERF have contributed significantly to health risk assessment of radiation exposure by international organizations. In particular, the findings have played a central role as a source of information on assessments of the latest findings regarding radiation health risks for the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Among the many studies in the world that provide basic data in this area, ABCC-RERF research represents the most reliable and comprehensive information on radiation health risks through accurate dose estimates and long-term incidence and mortality follow-up studies.

Risk assessment by UNSCEAR has provided the scientific basis for recommendations by the International Commission on Radiological Protection (ICRP) regarding radiation protection standards for radiation workers and the general public and for international standards established by the International Atomic Energy Agency (IAEA), as well as laws and regulations in various countries.

ABCC-RERF research results have also played an important role in assessment carried out by the Committee on Biological Effects of Ionizing Radiation (BEIR) of the U.S. National Research Council (NRC), which conducts risk assessment similar to that of UNSCEAR.

Contribution of ABCC-RERF research to risk assessment by UNSCEAR

Since its establishment in December 1955, UNSCEAR has carried out detailed examination of data on radiation health risks obtained throughout the world, evaluated the results scientifically, and published comprehensive reports, including more than 20 major reports. Its first report, published in 1958, already included a summary of the leukemia risks in Hiroshima and Nagasaki. Subsequent reports, most of which were based on the results of ABCC-RERF analyses, introduced many findings from the studies of A-bomb survivors in Hiroshima and Nagasaki.

In 2008, the UNSCEAR 2006 Report, Vol. I, which included reports titled "Epidemiological studies of radiation and cancer" and "Epidemiological evaluation of cardiovascular disease and other noncancer diseases following radiation exposure," was published. With regard to cancer, results from mortality studies (1950–2000) and incidence studies (1958–1998) based on LSS analysis using DS02 were prominent sections of that volume. Findings involving the LSS in the UNSCEAR report included: 1) In risk analysis using the new DS02, solid cancer risk decreased by about 7% compared with analysis based on DS86, but there were no changes in the patterns of dose response or temporal variation in risk; 2) Due to extension of the follow-up period and the resulting increase in number of cancer cases, the accuracy of statistical estimation has improved, making it possible to examine the shape of the dose-response curve at even lower doses. Further extension of the follow-up period will provide more information on low-dose risks; and 3) Extension of the follow-up period has shed light on long-term risks after exposure, especially risks among those exposed at young ages.

In this report, UNSCEAR conducted its own analysis using mortality and cancer incidence data published by RERF, and investigated the minimum doses at which risk increases could be detected.

For the report on noncancer diseases, the results obtained by RERF in the LSS and the AHS have proven to be valuable. The report concludes that the data currently available are insufficient to prove a causal relationship between exposure to radiation of up to 1–2 Gy and cardiovascular diseases, because as of 2006, the only data showing an association between exposure to those levels of exposure and fatal cardiovascular diseases are A-bomb survivor data in Japan, because there is no consistency among the results from other studies, and because details of related biological mechanisms are unknown.

Results of the health effects studies on A-bomb survivors also played an important role in the section titled "Effects of ionizing radiation on the immune system" in the UNSCEAR 2006 Report, Vol. II. Furthermore, with respect to the effects of radiation exposure in children, the findings from the LSS and AHS conducted by RERF are featured prominently in the UNSCEAR 2013 Report, Vol. II.

Contribution of ABCC-RERF research to ICRP

ICRP, an international organization that makes recommendations on radiation protection from the standpoint of specialists, was founded in 1928. ICRP has published numerous reports on issues related to radiation protection. In particular, the organization compiled basic guidelines concerning radiation protection and issued major recommendations in 1958, 1964, 1966, 1977, 1990, and more recently in 2007. Although ICRP does not have binding legal authority, its recommendations are internationally authorita-

tive and have served as the basis for IAEA safety standards, as well as laws, ordinances, and guidelines regarding radiation protection in numerous countries worldwide.

One example of use of the results of health effects studies of A-bomb radiation in the preparation of major ICRP recommendations is a reduction of the annual dose limit for radiation workers that appeared in the organization's 1990 recommendations. The annual dose limit of 50 mSv for workers, which was established in 1956, remained effective until 1990, when it was reduced to an annual average of 20 mSv over the course of five years (or up to 50 mSv for any one of those years) based on the risk estimates obtained from the LSS data collected by ABCC-RERF through 1985.

In the ICRP 2007 recommendations, results of the cancer incidence studies (1958–1998) based on analysis using DS02 also played an important role. These major recommendations focused on incidence data because those data were thought to provide more reliable estimates of cancer risks. The cancer risk estimates in the 1990 recommendations were applied to the major 2007 recommendations, and inclusion of cancer incidence data from the LSS provided a stronger basis for risk modeling.

As described above, ABCC-RERF research achievements accumulated over many years have served as the core sources of information for past UNSCEAR reports and major ICRP recommendations, and their importance is expected to continue into the future. Given such responsibility, RERF takes seriously its obligation to continue releasing fair, neutral, and accurate scientific information.

【8】 Collaborative research programs

Domestic and international collaborative studies

RERF engages in collaborative projects together with external research organizations in Japan and overseas for expansion of the foundation's breadth of research and confirmation of the research results from its studies of A-bomb survivors.

An epidemiological project carried out in collaboration with the U.S. National Cancer Institute (NCI) as one of RERF's major international collaborative studies has continued for many years and generated numerous manuscripts on radiation effects, while providing frequent opportunities for researcher exchanges between the organizations. Another large-scale collaborative research project in recent years focuses on radiation and immunity with support from the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

A partnership program on epidemiological and statistical research of A-bomb radiation effects is ongoing among the University of Washington (U.S.), Kurume University (Japan), and RERF. This program has produced several manuscripts, created opportunities for researcher exchange, and contributed to the education of young scientists through lectures by RERF researchers for university graduate students.

RERF takes part in the Asian Cohort Consortium (ACC), a large cohort study organized by the U.S. Fred Hutchinson Cancer Research Center, participating in several studies of low-incidence cancers and so on. RERF is also engaged in the Thyroid Studies Collaboration, consisting of 17 cohorts numbering about 70,000 people in such locations as Europe, America, Australia, and Asia, with the aim of studying from various perspectives the risks caused by abnormal thyroid function.

In addition, RERF conducts studies and has produced numerous papers in collaboration with the University of Oxford (U.K.), Maastricht University (Netherlands), University of Rochester (U.S.), University of Hong Kong (China), National Institute on Aging (U.S.), Helmholtz Institute (Germany), and others.

【9】 Research review

From planning of research to publication of results

1. Research protocol preparation

Scientific research at RERF is initiated, in principle, on the basis of approval of research protocols (RPs). Proposed RPs are reviewed by the Research Protocol Review Committee and the Human Investigation Committee, and when appropriate, by the Ethics Committee for Genome Research, the Committee on Biological Samples, the Recombinant DNA Experiment Safety Committee, and the Experimental Animal Care Committee. RPs are ultimately reviewed and approved by the Executive Committee. Likewise, in the case of collaborative studies with external researchers, RPs must be prepared and reviewed by various committees before data are shared. Through such procedures for internal and external scientific review, this system provides assurance of scientific relevance and quality of the RPs, guards against the exploitation of human study participants, and ensures that high standards of ethics are met and that personal information is strictly protected.

The basic data collected through long-term follow-up studies such as the LSS, AHS, and studies of children of A-bomb survivors are designated separately as platform protocols.

2. Study conduct and scientific review (Scientific Advisory Committee)

When ABCC was reorganized into RERF in 1975, the need to continue research based on full partnership between Japan and the United States was reaffirmed. At this time, the Scientific Council, consisting of experts from Japan as well as the United States, was established to review the appropriateness of research and to make recommendations. The Scientific Council was renamed as the Scientific Advisory Committee when RERF changed its status to a public interest incorporated foundation in 2011, and this Committee continues to function today.

The objectives of the Scientific Advisory Committee are to review RERF's scientific research programs and make recommendations to the RERF Board of Directors and Board of Councilors with respect to direction of new research programs, and/or continuation or alteration of programs in progress. The Scientific Advisory Committee consists of U.S. and Japanese experts in RERF's research fields, including medicine, epidemiology, radiobiology, genetics, and statistics. The Scientific Advisory Committee currently has 10 members, five from the United States and five from Japan. These Scientific Advisors are each appointed to serve a five-year term and may be reappointed once. To achieve close assessment of RERF's research programs, the Scientific Advisors serve two terms whenever possible, with one member each from the United States and Japan being replaced every year. The independence and neutrality of the Scientific Advisors is respected, and the Committee operates under the leadership of two co-chairs, one Japanese citizen and one U.S. citizen, who are selected from among the members.

The Scientific Advisory Committee convenes once a year to receive a report on RERF's scientific activities, to visit research departments for presentations from research scientists, and to review research activities. Detailed review results are compiled into a report, and the evaluation and recommendations are presented by one of the co-chairs to the Board of Councilors. A new review method has recently been introduced in which designated research departments undergo an in-depth review on a three-year, rotating basis. For this review, when necessary, experts in relevant research fields are invited to serve as Special Scientific Advisors.

3. Publication of study results

Scientific papers are prepared on the basis of study results. Through arrangement by the Scientific Reports Review Committee, RERF research scientists specializing in the fields concerned, and external specialists if needed, review scientific papers, and the RERF chairman grants final approval for submission of manuscripts to scientific journals. Upon approval, the manuscripts are submitted to scientific journals in Japan as well as abroad. Prior to publication in such journals, the scientific papers undergo review by the journal reviewers.

In this way, RERF research findings are widely publicized and distributed worldwide through publication in national and international journals, through publication as technical books, and through oral and poster presentations at national and international scientific meetings.

Data for risk estimation of A-bomb-related cancers that are used in reports from major studies such as the LSS can be downloaded from the RERF website, making it possible to recalculate risk estimates for verification. These data are made available in a form ensuring that individuals cannot be identified. All such personal information is closely safeguarded by RERF.

【10】 Research materials

Archiving epidemiological data and biological samples

The ABCC-RERF LSS cohort is a fixed population consisting of individuals covering a wide age range. When the LSS follow-up is completed, RERF will possess a database of medical information obtained through a lifetime follow-up study following radiation exposure of one of the largest fixed cohorts in the world representative of a general population.

In addition, RERF stores biosamples such as blood, blood fractions, and urine collected at the time of health examinations from the AHS population and from the F_1 Clinical Study population comprising children of A-bomb survivors. When this collection process is completed, RERF will possess an important historic research resource for elucidating radiation health effects and for conducting other medical research, permitting retrospective analysis of clinical samples for understanding the natural history of diseases following observation of all health events.

1. Archiving epidemiological data

The recorded data obtained through cohort studies such as the LSS, AHS, *in utero* study, and F_1 study consist of basic information regarding the subjects (name, date of birth, sex, permanent domicile, A-bomb exposure conditions, etc.), death information, cancer incidence information, information from medical interviews with AHS and F_1 Clinical Study subjects including medical histories, and health examination results such as diagnosis and observations, electrocardiographic findings, X-ray images, and so on. While these cohort members are alive, the volume of such information continues to increase. Since all such data represent confidential personal information, they are strictly safeguarded, with the majority of the information coded and stored electronically. These epidemiological data have been stored as electronic information since the establishment of ABCC. The system has progressed, beginning with the punched-card system, then mainframe computers, and evolving into the present-day workstation-based distributed processing system. RERF started using a network system in 1985. By the early 1990s, this system was completed and covered the entire foundation, significantly contributing to integrated management of data on a foundation-wide basis.

2. Management of epidemiological data

RERF databases are classified into two independent and separately managed categories: resource-management databases and research databases. As a result, 1) the burden on database servers is reduced, 2) direct effects on research databases can be avoided from additions and changes of examination items to the resource-management databases requested by both the Departments of Epidemiology and Clinical Studies, and 3) personal information leaks are prevented more rigorously by using completely different ID numbers for the two types of databases.

These databases are managed in an integrated manner based on their respective ID numbers, and data transfers and links between the databases are carried out fully automatically while personal information protections are enforced at a high level.

3. Storage of biosamples

Biosamples from the AHS and F_1 Clinical Study participants are stored in ultra-low temperature deep freezers at –80°C (about 75 deep freezers in Hiroshima and about 25 in Nagasaki) or in large automated liquid nitrogen storage tanks (liquid/vapor phase) at approximately –190°C. For a portion of these biosamples, single samples were divided for storage in both Hiroshima and Nagasaki.

On April 1, 2013, the Biosample Center was established with full-time staff assigned to manage biosamples in an integrated fashion and to make them more readily available to researchers.

Biosamples stored at the Biosample Center are defined as the following:

- ✧ Blood samples: Serum and lymphocyte samples donated by AHS and F_1 Clinical Study participants.
- ✧ Urine samples: Urine samples donated by AHS and F_1 Clinical Study participants.
- ✧ Pathological samples: Pathological tissue samples from surgery or autopsies are stored as paraffin embedded blocks or stained slides. In collaboration with pathologists at major hospitals in Hiroshima and Nagasaki, RERF has begun to construct an archival system for surgical cancer samples from A-bomb survivors.
- ✧ Cytogenetic samples: Slides of chromosome spreads derived from blood lymphocytes of the subjects in the AHS and the F_1 Clinical Study.
- ✧ Extracted teeth: Teeth collected from individuals of the AHS cohort for the purpose of estimating radiation doses using ESR.

These biosamples stored at the Center are made available for use by investigators both inside and out-

side of RERF. Additional biosamples used in ongoing studies are entrusted to the Center by the responsible investigators for temporary safekeeping. Moreover, the Center is responsible for, as a rule, 1) preparation of biosamples, 2) duties associated with storage and use of biosamples, and 3) development and management of a biosample-related database system that is accessible by the public.

For storage of such biosamples, an emergency management system has been established that includes backup electric power generators in case of suspension of electrical power and temperature-monitoring devices affixed to each of the deep freezers.

4. Use of biosamples

Biosamples stored at RERF are used with strict consideration given to protection of personal information in compliance with regulations and guidelines concerning research ethics. As it continues to establish regulations pertaining to policies, procedures, and other matters regarding the use of these integrated but limited biosamples, RERF will establish procedures involving how to make databases available to the public, and how research protocols using such biosamples should be screened and approved, based on the consensus of society. These efforts are expected to result in broader use of RERF's globally unique research resources.

Research departments

Department of Clinical Studies

The Department of Clinical Studies conducts follow-up studies of participants in the AHS, which is a selected subset of the LSS and *in utero* cohorts, in order to focus analysis on the relationship between radiation and the development of noncancer diseases. Currently, studies based on comprehensive health examinations are also conducted to follow the F_1 clinical cohort.

In addition to standardized health examinations and routine laboratory tests of blood and urine, special tests are conducted to evaluate endocrine diseases, gynecological diseases, skeletal and cognitive impairments, ophthalmological diseases, cardiovascular abnormalities, and so on. Thus, the AHS is among the most comprehensive clinical follow-up studies of radiation effects ever undertaken. Examinations are voluntary, and participation rates are regularly as high as 70%–80%. All of the clinical and epidemiological data and biological specimens are stored for utilization in health effects studies.

Participants are fully informed of examination results, which are used for referral to local physicians when necessary. In this way, health examination studies are conducted not only for the purpose of clinical and epidemiological research but also to contribute to the long-term assessment of the health status of A-bomb survivors and maintenance of their health.

Department of Molecular Biosciences

The Department of Molecular Biosciences performs basic science research involving studies of genetic effects and carcinogenesis mechanisms. Using blood specimens provided by survivors and their children, the department is investigating whether or not mutation frequencies in offspring are affected by parental radiation exposure. Utilizing molecular biological techniques, the department is also examining mutations of oncogenes and tumor suppressor genes in cancer tissue specimens (thyroid, colon, and lung) stored over several decades at RERF or at local hospitals in Hiroshima and Nagasaki.

The department is also making efforts to identify and evaluate biomarkers linking radiation exposure to diseases among A-bomb survivors. Biomarkers currently being assessed involve immune functions, genetic factors, unrepairable DNA radiation damage, DNA methylation, and transcription. Chromosome aberrations in lymphocytes as well as the electron spin resonance signals from tooth enamel are also assessed to provide information on uncertainties in individual doses calculated by DS02.

Department of Epidemiology

The Department of Epidemiology has the primary task of clarifying through epidemiological studies the risks associated with radiation exposure in humans. For almost 60 years, follow-up studies of more than 200,000 survivors and their children have been conducted through the LSS cohort of A-bomb survivors, the cohort of people who were *in utero* at the time of the bombings, and the F_1 cohort of persons conceived after the bombings. Analyses focus on mortality and cancer incidence in relation to radiation dose, allowing for risk factors other than radiation. The LSS is the most important epidemiological study of radiation effects in humans in the world because of the size and well-characterized nature of the study population, the wide range of radiation doses and ages, and the duration and completeness of the follow-up studies. The *in utero* and F_1 cohorts are the only such fixed cohorts in the world with follow-up into the adult years.

The department is also entrusted by the governments of Hiroshima City, Hiroshima Prefecture, and Nagasaki Prefecture to manage local tumor registries. The collected data serve as a unique source of information on cancer incidence for both A-bomb survivors and the general population.

Department of Statistics

The Department of Statistics analyzes information collected by other departments on radiation effects, provides statistical support and advice to research scientists in other RERF departments, and assists with data management. Members of the department aid in designing studies and develop and apply statistical procedures appropriate for analyzing RERF's unique research data. Management of the dose information and calculation of individual doses are further responsibilities of the department.

Department of Information Technology

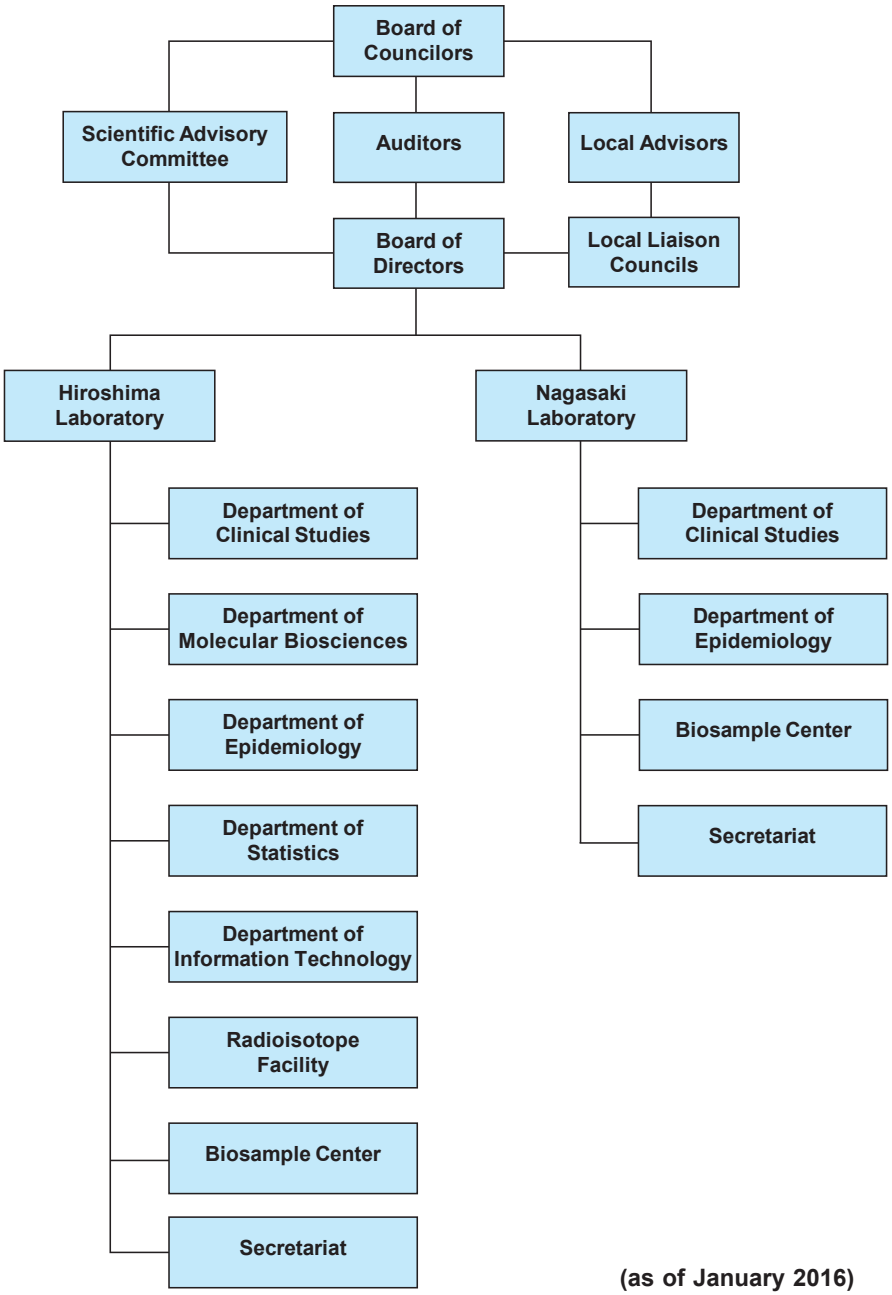
The Department of Information Technology comprises the Systems Technology Section and the Library and Archives Section.

The Systems Technology Section provides, maintains, and integrates RERF computers, maintains the RERF network under secure conditions, and develops various databases and database application programs necessary for RERF researchers. The section is also involved in technological cooperation in various fields both inside and outside of Japan.

The Library and Archives Section supervises RERF's professional library, with its focus on radia-

tion medicine and biology, and carries out work related to the publication of RERF research papers in scientific journals. The section records and manages research papers and academic meeting presentations, as well as collects, stores, and makes available for perusal other important ABCC-RERF archival materials. It also responds to inquiries and requests for distribution from both inside and outside of RERF regarding the above papers and documents.

Organization of RERF



(as of January 2016)

Glossary

Physical dose

The gray (Gy; 1 Gy = 1,000 mGy) is a unit used to measure radiation dose. One gray is equal to 1 joule absorption per kilogram of a given material. One gray is equal to 100 rad (rad, or 100 erg per gram, is a unit previously used to measure radiation dose).

Weighted absorbed organ dose

The majority of A-bomb radiation that reached the ground consisted of γ rays, with a small fraction of neutrons that accounted for only a small percentage of the total dose. Because neutrons affect living tissue more strongly than do γ rays per unit dose, RERF uses, for each organ, weighted absorbed dose, which is the sum of the neutron dose multiplied by 10 (a weighting factor that reflects its greater impact) and the γ-ray dose. Weighted absorbed dose is useful for expressing a more biologically meaningful dose. For example, if the colon received 1 Gy of γ rays and 0.1 Gy of neutrons, the weighted absorbed colon dose would be $1 + 0.1 \times 10 = 2$ Gy. Weighted absorbed dose is the same as the commonly used equivalent dose and was once expressed in units of Sv, a unit used for equivalent dose. However, RERF now uses weighted absorbed organ dose, expressed in units of Gy, because the unit for the effective dose is also the sievert (Sv). Effective dose, which is the equivalent dose weighted for varying degrees of radio-sensitivity of individual tissues and organs exposed to radiation, is used as an indicator for the purpose of radiation protection.

Relative risk (RR)

Relative risk is used here to refer to the ratio of risk (mortality or incidence) from an event occurring among members of a population exposed to radiation relative to that in an unexposed population, or control population. An RR of 1 implies that exposure has had no effect on risk.

$$\text{Relative risk (RR)} = \frac{\text{Mortality (incidence) in radiation-exposed population}}{\text{Mortality (incidence) in unexposed population}}$$

Excess relative risk (ERR)

Excess relative risk is used here to refer to the increase in the ratio of an event (mortality or incidence) occurring among members of a population exposed to radiation as compared to that in an unexposed population. In other words, ERR is the value of RR minus 1, indicating how many times risk is increased with radiation exposure.

$$\text{Excess relative risk (ERR)} = \frac{\text{Mortality (incidence) in radiation-exposed population}}{\text{Mortality (incidence) in unexposed population}} - 1$$

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

Excess absolute rate is calculated by subtracting mortality (or incidence) in an unexposed population from mortality (or incidence) among members of a population exposed to radiation. In other words, EAR is the absolute value of the increase in rate.

Excess absolute rate (EAR) = (Mortality or incidence rate in radiation-exposed population) – (Mortality or incidence rate in unexposed population)

Attributable fraction

Attributable fraction is used here to refer to the increase in proportion in the outcome rate of mortality or disease incidence due to radiation exposure in the population under observation. An estimated model is used for calculation. Total attributable fraction for leukemia, for example, is estimated to be nearly 50%, and for solid cancers a little less than 10%, among LSS survivors who received ≥0.005 Gy. Estimated attributable fraction (in total) measures the excess event rate in the LSS cohort that is assumed to be attributable to radiation exposure. It should be noted that the attributable fraction varies depending on radiation dose distribution, sex/age distribution, and other factors within the cohort. It is also known as population attributable fraction.

Attributable fraction = the proportion of the total number of events or the overall rate due to the exposure observed in the entire cohort, including exposed and nonexposed, that is in excess (ERR) above the number or rate in the nonexposed

Prevalence versus 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).

Hypocenter

Hypocenter refers to the location on the ground directly below the bomb air-burst point.

Proximally versus distally exposed

According to the definition used to establish the LSS cohort, persons exposed to the atomic bombings within 2.5 km of the hypocenters are referred to as proximally exposed, and those at distances of 2.5 to 10 km as distally exposed. Since the average estimated radiation dose for those exposed at approximately 2.5 km of the hypocenter in Hiroshima and those at 2.7 km in Nagasaki is 5 mGy, the figure of 5 mGy is sometimes used as the line of demarcation between proximally and distally exposed groups. In more general applications, these terms are sometimes used with no specific reference to the above definitions.

References

【2】 Radiation effects on human health: Acute deaths and acute effects

1. Sasaki H, Ito C, Kamada N, Shigematsu I: Acute death and acute effects. Hiroshima International Council for Medical Care of the Radiation-exposed, ed. Effects of A-bomb Radiation on the Human Body, 2nd Edition. Tokyo: Bunkodo; 2012. pp 10–3. (Japanese)
2. Fujita S, Kato H, Schull WJ: The LD_{50} associated with exposure to the atomic bombing of Hiroshima and Nagasaki. J Radiat Res 1991; 32(Suppl):154–61.
3. Kusama T, Kai N, Ban N: Radiation and Health Sciences. Tokyo: Kyorin Shoin; 1995. (Japanese)
4. Stram DO, Mizuno S: Analysis of the DS86 atomic bomb radiation dosimetry methods using data on severe epilation. Radiat Res 1989; 117:93–113.

【4】 Radiation dosimetry

【A】 Physical dose measurements

1. Dosimetry system and residual radiation

5. Okajima S, Fujita S, Harley JH: Radiation doses from residual radioactivity. Roesch W, ed. US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki Final Report. Volume 1. Hiroshima: Radiation Effects Research Foundation; 1987. pp 205–26.
6. NHK Hiroshima Bureau, A-bomb Project Team, Maruyama T, Kato H, Watanabe T, et al.: 42 Years of Residual Radioactivity in Hiroshima—Path of an A-bomb Relief Party. Tokyo, NHK Publishing Co., Ltd.; 1988. (Japanese)
7. Okajima S, Takeshita K, Antoku S, et al.: Effects of the radioactive fallout of the Nagasaki atomic bomb. ABCC Technical Report 12−75. 1975.

2. Biological effects of internal exposure

8. Little MP, Hall P, Charles MW: Are cancer risks associated with exposures to ionising radiation from internal emitters greater than those in the Japanese A-bomb survivors? Radiat Environ Biophys 2007; 46:299–310.
9. Lee W, Chiacchierini RP, Shleien B, et al.: Thyroid tumors following ^{131}I or localized X irradiation to the thyroid and pituitary glands in rats. Radiat Res 1982; 92:307–19.
10. Ron E, Lubin JH, Shore RE, et al.: Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. Radiat Res 1995; 141:259–77.
11. Tronko MD, Howe GR, Bogdanova TI, et al.: A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: Thyroid cancer in Ukraine detected during first screening. J Natl Cancer Inst 2006; 98:897–903.
12. Zablotska LB, Ron E, Rozhko AV, et al.: Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. Br J Cancer 2011; 104:181–7.
13. Brenner AV, Tronko MD, Hatch M, et al.: I-131 dose response for incident thyroid cancers in Ukraine related to the Chornobyl accident. Environ Health Perspect 2011; 119:933–9.

【B】 Biological dosimetry

1. Chromosome aberrations

14. Kodama Y, Pawel D, Nakamura N, et al.: Stable chromosome aberrations in atomic bomb survivors: Results from 25 years of investigation. Radiat Res 2001; 156:337–46.

2. Electron spin resonance (ESR) using tooth enamel

15. Nakamura N, Miyazawa C, Sawada S, et al.: A close correlation between electron spin resonance (ESR) dosimetry from tooth enamel and cytogenetic dosimetry from lymphocytes of Hiroshima atomic-bomb survivors. Int J Radiat Biol 1998; 73:619–27.
16. Nakamura N, Cullings HM, Kodama Y, et al.: A method to differentiate between the levels of ESR signals induced by sunlight and by ionizing radiation in teeth from atomic bomb survivors. Radiat Res 2006; 165:359–64.

【5】 Radiation effects on human health: Late effects

【A】 Results from studies of A-bomb survivors

17. Ozasa K, Shimizu Y, Suyama A, et al.: Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: An overview of cancer and noncancer diseases. Radiat Res 2012; 177:229–43.
18. Yamada M, Wong FL, Fujiwara S, et al.: Noncancer disease incidence in atomic bomb survivors, 1958–1998. Radiat Res 2004; 161:622–32.

1. Malignant tumors

(1) Leukemia and related diseases

(See also reference17.)

19. Hsu WL, Preston DL, Soda M, et al.: The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. Radiat Res 2013; 179:361–82.
20. Preston DL, Kusumi S, Tomonaga M, et al.: Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 1994; 137(2 Suppl):S68–97.
21. Iwanaga M, Hsu WL, Soda M, et al.: Risk of myelodysplastic syndromes in people exposed to ionizing radiation: A retrospective cohort study of Nagasaki atomic bomb survivors. J Clin Oncol 2011; 29:428–34.

(2) Solid cancers

(See also reference 17.)

22. Preston DL, Ron E, Tokuoka S, et al.: Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007; 168:1–64.

(3) Site-specific cancer risks

a. Stomach cancer

(See also references 17 and 22.)

23. Sauvaget C, Lagarde FAA, Nagano J, et al.: Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). Cancer Causes Control 2005; 16:773–80.
24. Hayashi T, Ito R, Cologne JB, et al.: Effects of *IL-10* haplotype and atomic bomb radiation exposure on gastric cancer risk. Radiat Res 2013; 180:60–9.

b. Colorectal cancer

(See also references 17 and 22.)

25. Semmens EO, Kopecky KJ, Grant EJ, et al.: Relationship between anthropometric factors, radiation exposure, and colon cancer incidence in the Life Span Study cohort of atomic bomb survivors. Cancer Causes Control 2013; 24:27–37.

c. Liver cancer

(See also reference 22.)

26. Sharp GB, Mizuno T, Cologne JB, et al.: Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. Int J Cancer 2003; 103:531–7.
27. Ohishi W, Fujiwara S, Cologne JB, et al.: Impact of radiation and hepatitis virus infection on risk of hepatocellular carcinoma. Hepatology 2011; 53:1237–45.

d. Lung cancer

(See also references 17 and 22.)

28. Furukawa K, Preston DL, Lonn S, et al.: Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. Radiat Res 2010; 174:72–82.

e. Breast cancer

29. Land CE, Tokunaga M, Koyama K, et al.: Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiat Res 2003; 160:707–17.
30. Land CE, Hayakawa N, Machado SG, et al.: A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. Cancer Causes Control 1994; 5:167–76.
31. McDougall JA, Sakata R, Sugiyama H, et al.: Timing of menarche and first birth in relation to risk of breast cancer in A-bomb survivors. Cancer Epidemiol Biomarkers Prev 2010; 19:1746–54.
32. Tokuoka S, Asano M, Yamamoto T, et al.: Histologic review of breast cancer cases in survivors of atomic bombs in Hiroshima and Nagasaki, Japan. Cancer 1984; 54:849–54.

f. Urinary organ cancer

(See also references 17 and 22.)

33. Grant EJ, Ozasa K, Preston DL, et al.: Effects of radiation and lifestyle factors on risks of urothelial carcinoma in the Life Span Study of atomic bomb survivors. Radiat Res 2012; 178:86–98.

g. Brain and central nervous system tumors

(See also reference 22.)

34. Preston DL, Ron E, Yonehara S, et al.: Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst 2002; 94:1555–63.

h. Thyroid cancer

(See also reference 22.)

35. Socolow EL, Hashizume A, Neriishi S, et al.: Thyroid carcinoma in man after exposure to ionizing radiation. A summary of the findings in Hiroshima and Nagasaki. N Engl J Med 1963; 268:406–10.
36. Furukawa K, Preston D, Funamoto S, et al.: Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. Int J Cancer 2013; 132:1222–6.
37. Imaizumi M, Usa T, Tominaga T, et al.: Radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors 55–58 years after radiation exposure. JAMA 2006; 295:1011–22.
38. Hayashi Y, Lagarde F, Tsuda N, et al.: Papillary microcarcinoma of the thyroid among atomic bomb survivors: Tumor characteristics and radiation risk. Cancer 2010; 116:1646–55.
39. Hamatani K, Eguchi H, Ito R, et al.: *RET/PTC* rearrangements preferentially occurred in papillary thyroid cancer among atomic bomb survivors exposed to high radiation dose. Cancer Res 2008; 68:7176–82.
40. Hamatani K, Mukai M, Takahashi K, et al.: Rearranged anaplastic lymphoma kinase (*ALK*) gene in adult-onset papillary thyroid cancer amongst atomic bomb survivors. Thyroid 2012; 22:1153–9.

2. Noncancer diseases and abnormalities (excluding deaths due to blood diseases)

(See also references 17 and 18.)

41. Kubo M, Kiyohara Y, Kato I, et al.: Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: The Hisayama Study. Stroke 2003; 34:2349–54.

(1) Mortality and incidence of circulatory disease (heart disease and stroke)

(See also reference 18.)

42. Shimizu Y, Kodama K, Nishi N, et al.: Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ 2010; 340:b5349.
43. Takahashi I, Abbott RD, Ohshita T, et al.: A prospective follow-up study of the association of radiation exposure with fatal and non-fatal stroke among atomic bomb survivors in Hiroshima and Nagasaki (1980–2003). BMJ Open 2012; 2:e000654.
44. Wong FL, Yamada M, Sasaki H, et al.: Effects of radiation on the longitudinal trends of total serum cholesterol levels in the atomic bomb survivors. Radiat Res 1999; 151:736–46.
45. Sera N, Hida A, Imaizumi M, et al.: The association between chronic kidney disease and cardiovascular disease risk factors in atomic bomb survivors. Radiat Res 2013; 179:46–52.

(2) Mortality and incidence of liver disease

(See also reference 18.)

46. Shimizu Y, Pierce DA, Preston DL, et al.: Studies of the mortality of atomic bomb survivors. Report 12, part II. Noncancer mortality: 1950–1990. Radiat Res 1999; 152:374–89.
47. Shimizu Y, Kato H, Schull WJ, et al.: Studies of the mortality of A-bomb survivors. 9. Mortality, 1950–1985: Part 3. Noncancer mortality based on the revised doses (DS86). Radiat Res 1992; 130:249–66.
48. Preston DL, Shimizu Y, Pierce DA, et al.: Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003; 160:381–407.
49. Sharp GB, Mizuno T, Fukuhara T, et al.: Lack of association between acute exposure to ionizing radiation and liver cirrhosis. Int J Radiat Biol 2006; 82:231–40.
50. Beebe GW, Yamamoto T, Matsumoto YS: ABCC-JNIH pathology studies, Hiroshima-Nagasaki. Report 2. October

1950–December 1965. ABCC Technical Report 8−67. 1967.
51. Schreiber WM, Kato H, Robertson JD: Cirrhosis of the liver, Hiroshima-Nagasaki, 1 October 1961–31 December 1967. ABCC Technical Report 17−69. 1969.
52. Asano M, Kato H, Yoshimoto K, et al.: Primary liver carcinoma and liver cirrhosis in atomic bomb survivors, Hiroshima and Nagasaki, 1961–75, with special reference to hepatitis B surface antigen. J Natl Cancer Inst 1982; 69:1221–7.
53. Wong FL, Yamada M, Sasaki H, et al.: Noncancer disease incidence in the atomic bomb survivors: 1958–1986. Radiat Res 1993; 135:418–30.

(3) Thyroid disease

(See also reference 37.)

54. Shimura H: Frequency and course of thyroid tumors in Japan: Data from complete medical examinations. Nihon Kojosen Gakkai Zasshi [J Jpn Thyroid Assoc] 2010; 1:109–13. (Japanese)

(4) Cataract

55. Cogan DG, Donaldson DD: Experimental radiation cataracts. I. Cataracts in the rabbit following single X-ray exposure. AMA Arch Ophthalmol 1951; 45:508–22.
56. Masuda Y: Current status of atomic bomb cataracts in Hiroshima. Nihon Ganka Gakkai Zasshi [Acta Soc Ophtalmol Jpn] 1955; 59:899. (Japanese)
57. Tokunaga T: Atomic bomb radiation cataract in Nagasaki. Nihon Ganka Gakkai Zasshi [Acta Soc Ophthalmol Jpn] 1959; 63:1211–30. (Japanese)
58. Tokunaga T: Remote study results on atomic bomb cataracts in Nagasaki. Nihon Ganka Gakkai Zasshi [Acta Soc Ophthalmol Jpn] 1968; 72:1774–81. (Japanese)
59. International Commission on Radiological Protection: 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann ICRP 21 (1−3); 1991.

(5) Gynecological disease

(See also reference 18.)

60. Sakata R, Shimizu Y, Soda M, et al.: Effect of radiation on age at menopause among atomic bomb survivors. Radiat Res 2011; 176:787–95.

(6) Physical growth and development and bone and locomotor apparatus disease

61. Nakashima E, Carter RL, Neriishi K, et al.: Height reduction among prenatally exposed atomic-bomb survivors: A longitudinal study of growth. Health Phys 1995; 68:766–72.
62. Nakashima E, Fujiwara S, Funamoto S, et al.: Effect of radiation dose on the height of atomic bomb survivors: A longitudinal study. Radiat Res 2002; 158:346–51.
63. Blackard WG, Seigel DG: Peripheral osteoporosis in the ABCC-JNIH Adult Health Study, Hiroshima-Nagasaki, November 1961–June 1962. ABCC Technical Report 17−63. 1963.
64. Ross PD, Fujiwara S, Huang C, et al.: Vertebral fracture prevalence in women in Hiroshima compared to Caucasians or Japanese in the US. Int J Epidemiol 1995; 24:1171–7.
65. Huang C, Ross PD, Fujiwara S, et al.: Determinants of vertebral fracture prevalence among native Japanese women and women of Japanese descent living in Hawaii. Bone 1996; 18:437–42.

(7) Skin disease

66. Committee for the Compilation of Materials on Damage Caused by the Atomic Bombs in Hiroshima and Nagasaki, ed. Hiroshima and Nagasaki: The Physical, Medical and Social Effects of the Atomic Bombings). Tokyo: Iwanami Shoten; 1979. (Japanese).
67. Hatano S, Watanuki K: Report on effects of the A-bombing of Hiroshima, with special reference to keloid formation. The Special Committee for the Investigation of the Effects of the Atomic Bomb, National Research Council of Japan, ed. Medical Report on Atomic Bomb Effects. Tokyo: Japan Society for the Promotion of Science; 1953. pp 621–31. (Japanese)
68. Shirabe R, Tezuka H: Burns and scars induced by A-bomb and treatment thereof. Hiroshima Igaku [J Hiroshima Med Assoc] 1959; 12:897–902. (Japanese)
69. Johnson MT, Land CE, Gregory PB, et al.: Effects of ionizing radiation on the skin, Hiroshima-Nagasaki. ABCC Technical Report 20−69. 1969.

(8) Psychoneurological and psychological effects

70. Yamada M, Kodama K, Wong FL: The long-term psychological sequelae of atomic-bomb survivors in Hiroshima and Nagasaki. Ricks RC, Berger ME, O'Hara FM, eds. The Medical Basis for Radiation-Accident Preparedness III. The Psychological Perspective. Amsterdam: Elsevier; 1991. pp 155–63.
71. Yamada M, Izumi S: Psychiatric sequelae in atomic bomb survivors in Hiroshima and Nagasaki two decades after the explosions. Soc Psychiatry Psychiatr Epidemiol 2002; 37:409–15.
72. Beebe GW, Kato H, Land CE: JNIH-ABCC Life Span Study, Hiroshima-Nagasaki. Report 5. Mortality and radiation dose, October 1950–September 1966. ABCC Technical Report 11−70. 1970.

3. Abnormality in the immune system and inflammation

73. Kusunoki Y, Yamaoka M, Kasagi F, et al.: T cells of atomic bomb survivors respond poorly to stimulation by Staphylococcus aureus toxins in vitro: Does this stem from their peripheral lymphocyte populations having a diminished naïve CD4 T-cell content? Radiat Res 2002; 158:715–24.
74. Kusunoki Y, Yamaoka M, Kasagi F, et al.: Long-lasting changes in the T-cell receptor V beta repertoires of CD4 memory T-cell populations in the peripheral blood of radiation-exposed people. Br J Haematol 2003; 122:975–84.
75. Yamaoka M, Kusunoki Y, Kasagi F, et al.: Decreases in percentages of naïve CD4 and CD8 T cells and increases in percentages of memory CD8 T-cell subsets in the peripheral blood lymphocyte populations of A-bomb survivors. Radiat Res 2004; 161:290–8.
76. Hayashi T, Morishita Y, Kubo Y, et al.: Long-term effects of radiation dose on inflammatory markers in atomic bomb survivors. Am J Med 2005; 118:83–6.
77. Kusunoki Y, Hayashi T: Long-lasting alterations of the immune system by ionizing radiation exposure: Implications for disease development among atomic bomb survivors. Int J Radiat Biol 2008; 84:1–14.

78. Kusunoki Y, Yamaoka M, Kubo Y, et al.: T-cell immunosenescence and inflammatory response in atomic-bomb survivors. Radiat Res 2010; 174:870–6.
79. Hayashi T, Morishita Y, Khattree R, et al.: Evaluation of systemic markers of inflammation in atomic-bomb survivors with special reference to radiation and age effects. FASEB J 2012; 26:4765–73.

【B】 Results from studies of in utero survivors

1. Intellectual impairment

80. Otake M, Yoshimaru H, Schull WJ: Prenatal exposure to atomic radiation and brain damage. Cong Anom 1989; 29:309–20.
81. Otake M, Schull WJ, Yoshimaru H: Brain damage among the prenatally exposed. J Radiat Res 1991; 32(Suppl):249–64.

2. Growth impairment

82. Otake M, Schull WJ: Radiation-related small head sizes among prenatally exposed A-bomb survivors. Int J Radiat Biol 1993; 63:255–70.
83. Nakashima E: Relationship of five anthropometric measurements at age 18 to radiation dose among atomic bomb survivors exposed in utero. Radiat Res 1994; 138:121–6.

3. Malignant tumors

84. Preston DL, Cullings H, Suyama A, et al.: Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. J Natl Cancer Inst 2008; 100:428–36.

4. Noncancer diseases during adulthood

85. Tatsukawa Y, Nakashima E, Yamada M, et al.: Cardiovascular disease risk among atomic bomb survivors exposed *in utero*, 1978–2003. Radiat Res 2008; 170:269–74.

【C】 Results from studies of children of A-bomb survivors (genetic effects)

1. Birth defects (stillbirth, malformation, and neonatal death)

86. Neel JV, Schull WJ: The Children of Atomic Bomb Survivors: A Genetic Study. Washington, D.C.: National Academy Press; 1991.
87. Otake M, Schull WJ, Neel JV: Congenital malformations, stillbirths, and early mortality among the children of atomic bomb survivors: A reanalysis. Radiat Res 1990; 122:1–11.

2. Sex ratio

See reference 86.

3. Chromosome aberrations

88. Awa AA, Honda T, Neriishi S, et al.: Cytogenetic study of the offspring of atomic bomb survivors, Hiroshima and Nagasaki. Obe G, Basler A, eds. Cytogenetics: Basic and Applied Aspects. Berlin: Springer; 1987. pp 166–83.

4. Genetic effects studies at the protein level and subsequent DNA studies

(1) Blood protein mutations (1975–1985)

89. Neel JV, Satoh C, Hamilton HB, et al.: Search for mutations affecting protein structure in children of atomic bomb survivors: Preliminary report. Proc Natl Acad Sci (USA) 1980; 77:4221–5.
90. Neel JV, Satoh C, Goriki K, et al.: Search for mutations altering protein charge and/or function in children of atomic-bomb survivors: Final report. Am J Hum Genet 1988; 42:663–76.
91. Neel JV, Satoh C, Goriki K, et al.: The rate with which spontaneous mutation alters the electrophoretic mobility of polypeptides. Proc Natl Acad Sci (USA) 1986; 83:389–93.

(2) DNA studies (1985–present)

92. Kodaira M, Izumi S, Takahashi N, et al.: No evidence of radiation effect on mutation rates at hypervariable minisatellite loci in the germ cells of atomic-bomb survivors. Radiat Res 2004; 162:350–6.
93. Kodaira M, Ryo H, Kamada N, et al.: No evidence of increased mutation rates at microsatellite loci in offspring of A-bomb survivors. Radiat Res 2010; 173:205–13.
94. Asakawa J, Kuick R, Kodaira M, et al.: A genome scanning approach to assess the genetic effects of radiation in mice and humans. Radiat Res 2004; 161:380–90.
95. Takahashi N, Tsuyama N, Sasaki K, et al.: Segmental copy-number variation observed in Japanese by array-CGH. Ann Hum Genet 2008; 72:193–204.

5. Epidemiological and clinical studies

96. Kato H, Schull WJ, Neel JV: A cohort-type study of survival in the children of parents exposed to atomic bombings. Am J Hum Genet 1966; 18:339–73.
97. Neel JV, Kato H, Schull WJ: Mortality in the children of atomic bomb survivors and controls. Genetics 1974; 76:311–26.
98. Izumi S, Suyama A, Koyama K: Radiation-related mortality among offspring of atomic bomb survivors: A half-century of follow-up. Int J Cancer 2003; 107:292–7.
99. Yoshimoto Y, Neel JV, Schull WJ, et al.: Malignant tumors during the first 2 decades of life in the offspring of atomic bomb survivors. Am J Hum Genet 1990; 46:1041–52.
100. Izumi S, Koyama K, Soda M, et al.: Cancer incidence in children and young adults did not increase relative to parental exposure to atomic bombs. Br J Cancer 2003; 89:1709–13.

6. Prevalence of lifestyle diseases

101. Fujiwara S, Suyama A, Cologne JB, et al.: Prevalence of adult-onset multifactorial disease among offspring of atomic bomb survivors. Radiat Res 2008; 170:451–7.
102. Tatsukawa Y, Cologne JB, Hsu WL, et al.: Radiation risk of individual multifactorial diseases in offspring of the atomic-bomb survivors: A clinical health study. J Radiol Prot 2013; 33:281–93.

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