

Epidemiological research on radiation-induced cancer in atomic bomb survivors

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ABSTRACT

The late effects of exposure to atomic bomb radiation on cancer occurrence have been evaluated by epidemiological studies on three cohorts: a cohort of atomic bomb survivors (Life Span Study; LSS), survivors exposed *in utero*, and children of atomic bomb survivors (F₁). The risk of leukemia among the survivors increased remarkably in the early period after the bombings, especially among children. Increased risks of solid cancers have been evident since around 10 years after the bombings and are still present today. The LSS has clarified the dose-response relationships of radiation exposure and risk of various cancers, taking into account important risk modifiers such as sex, age at exposure, and attained age. Confounding by conventional risk factors including lifestyle differences is not considered substantial because people were non-selectively exposed to the atomic bomb radiation. Uncertainty in risk estimates at low-dose levels is thought to be derived from various sources, including different estimates of risk at background levels, uncertainty in dose estimates, residual confounding and interaction, strong risk factors, and exposure to residual radiation and/or medical radiation. The risk of cancer in subjects exposed *in utero* is similar to that in LSS subjects who were exposed in childhood. Regarding hereditary effects of radiation exposure, no increased risk of cancers associated with parental exposure to radiation have been observed in the F₁ cohort to date. In addition to biological and pathogenetic interpretations of the present results, epidemiological investigations using advanced technology should be used to further analyze these cohorts.

KEYWORDS: atomic bomb survivors, epidemiology, cancer

INTRODUCTION

The first two atomic bombs in human history targeted Hiroshima and Nagasaki and destroyed most of each city. In addition to injuries sustained due to the blast and the heat from the bombs, radiation exposure caused a wide array of acute symptoms, some of which induced death from gastrointestinal and bone marrow disturbances. It has been calculated that over 110 000 deaths in Hiroshima and 70 000 in Nagasaki occurred due to the atomic bombings within the year of 1945 [1]. Survivors of the physical injuries and acute radiation syndrome continue to suffer the stochastic effects and late-onset deterministic effects of atomic bomb radiation exposure.

The Atomic Bomb Casualty Commission (ABCC) was founded by the US National Academy of Sciences in 1947 to conduct research in the city of Hiroshima, with funding provided by the US Atomic Energy Commission. In 1948, ABCC established a second laboratory in Nagasaki. In the same year, the Japanese National Institute of Health of the Ministry of Health and Welfare joined the research

program. Since the late 1940s, many studies on the potential genetic effects of atomic bomb radiation exposure have been conducted in response to deep concern from both the public and scientists on the issue. Since the 1950s, individual doses of exposure to atomic bomb radiation among the survivors have been estimated using information about the physical properties of the atomic bombs, radiation physics, and individual shielding conditions at the time of exposure. In the mid-1950s, population-based fixed cohorts were constructed to investigate the late health effects of atomic bomb radiation over the survivors' and their children's lifetimes. These cohorts, which are still continuing today, consist of atomic bomb survivors, survivors who were exposed *in utero*, and children of atomic bomb survivors. They and several subcohorts have been followed-up in epidemiological studies; the subcohorts have participated in clinical examinations, as well [1].

In 1975, the Radiation Effects Research Foundation (RERF) was established as a binational non-profit foundation under Japanese

legislation, in accordance with an agreement between the governments of Japan and the USA. RERF succeeded all work at ABCC, and it transitioned into a public interest incorporated foundation in 2012 [1].

STUDY COHORTS

In the 1950 National Census of Japan, individuals were asked whether they had been in Hiroshima or Nagasaki at the time of the atomic bombings. Based on this information, the Life Span Study (LSS) cohort of atomic bomb survivors was established retrospectively. The LSS cohort was originally formed with ~100 000 members in the late 1950s and was expanded in 1968 and 1980 to reach the final number of ~120 000. It includes ~53 800 people who were exposed within 2.5 km of the hypocenters, ~39 900 exposed from 2.5 to 10 km, and ~26 600 who were not in either city at the time of the bombing. A majority of proximal survivors who were still within their exposure cities were selected into the LSS; distal survivors and not-in-city subjects were randomly selected into the cohort by matching for sex and age with the proximal survivors. All members were interviewed by ABCC personnel prior to recruitment into the cohort in order to determine their location and basic shielding information at the time of the bombing. Although the original LSS cohort was officially constructed in the late 1950s, a majority of the relevant information was collected via various surveys conducted by ABCC in the late 1940s and early 50s [1]. Members' vital statuses and causes of death were followed-up retrospectively between 1950 and each individual's respective enrollment date and prospectively thereafter. Follow-up of cancer incidence in Hiroshima and Nagasaki began in 1957 and 1958, respectively.

In 1958, the Adult Health Study (AHS) was formed with ~20 000 members who were selected from the LSS and were invited to participate in biennial health examinations at ABCC (and later at RERF). The total number of AHS members was later expanded to ~24 000, and ~20 600 of them have visited the clinic at least once. They have been asked to donate biosamples such as blood to the clinic for research purposes. An *in utero* cohort was formed with

~3600 survivors who had been exposed to atomic bomb radiation while in their mother's wombs. These members were selected for epidemiological studies alongside the LSS and have been followed-up retrospectively since 1945 (prospectively after their individual enrollment dates in the 1950–60s). About 1000 of these *in utero* cohort members were invited to join the AHS program in 1978. The F₁ cohort was formed from children who were born between 1946 and 1984 to at least one atomic bomb survivor or to two parents who were not in the city during the bombings; that is, children assumed to be conceived after the bombings. This cohort consists of ~76 800 members who have been followed-up in epidemiological studies since their birth (those who were enrolled in the early period were followed up retrospectively up to the time of enrollment, after which they were followed prospectively). Although no health effects have been seen in the F₁ population at this point, a health examination program for them began in 2002, the time when members began reaching the age at which cancer development and disease risk increases. Approximately 12 000 F₁ members are participating (Fig. 1) [1].

For all of these cohort members, ABCC-RERF has estimated individual doses of exposure to atomic bomb radiation as well as the risk of various diseases and health outcomes following exposure. Other, non-radiation risk factors for the outcomes under study were surveyed using six self-administered, mailed questionnaires between 1965 and 2008 (Fig. 1) [1].

EVALUATION OF RADIATION EXPOSURE

Radiation from the bombs can be classified into two types: initial radiation that was directly emitted from the bombs, and residual radiation. Residual radiation includes two types of radioactive products. The first is radiation emitted from induced radioisotopes in soil and metals activated by the bomb's neutrons; the second is nuclear fission products contained in radioactive fallout. Doses of initial radiation to which people were exposed depended on the physical properties of the bombs, distance from the epicenter, shielding conditions, and personal conditions such as body size, posture, and orientation to the epicenter. Atomic bomb survivors including both LSS and non-LSS

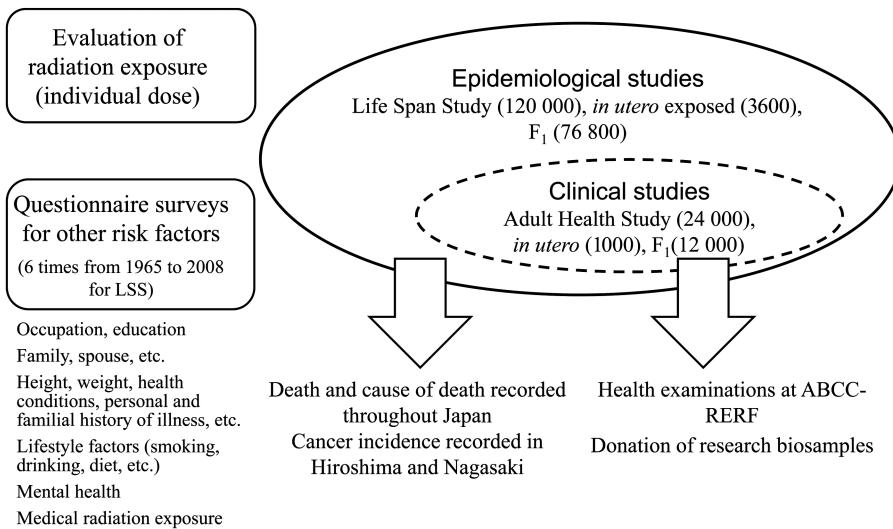


Fig. 1. Follow-up populations and evaluation of exposure and outcomes.

members were surveyed from the late 1940s onwards to collect basic information regarding location and simple shielding conditions at the time of the bombings. In the late 1950s, LSS members exposed to atomic bomb radiation within ~ 2 km of the hypocenters were asked to complete a second survey, this time to collect more detailed information about their exact position at the time of the bombings, e.g. precise locations on the maps, terrain conditions such as landforms, buildings and plants that may have shielded them from the explosions, layouts of houses and buildings, with survivors' positions if applicable, and individuals' posture and orientation to the epicenter. This information was used in order to accurately estimate their individual doses. For LSS members who did not complete this second survey (including those further from the hypocenters), simplified methods were applied; for example, the average transparency coefficient (a measure of shielding) for a wooden house, which was a typical Japanese abode in 1945, was calculated by the detailed estimation procedures mentioned above. This coefficient was then applied to members who were exposed in wooden houses in distal areas to estimate their individual doses. Individual doses for 15 organs were also estimated for a majority of LSS members. A weighted absorbed organ dose defined as neutron dose $\times 10$ + gamma dose in gray (Gy), where the coefficient 10 indicates the relative biological effectiveness of neutrons relative to gamma rays in atomic bomb radiation, has been used for risk estimation of exposure to atomic bomb radiation for analyses of health effects [2, 3].

The weighted free-in-air dose of radiation (non-shielded kerma) was estimated to be ~ 7 Gy and ~ 10 Gy at a ground distance of 1 km from the hypocenters in Hiroshima and Nagasaki, respectively. The dose fell sharply with increased distance from the hypocenters; the non-shielded kerma dose was 13 mGy at 2.5 km from the hypocenter in Hiroshima and 23 mGy in Nagasaki (Table 1). The average weighted absorbed colon dose was 1 Gy for people who were exposed at 1.1 km from the hypocenter in Hiroshima and 1.25 km in Nagasaki, and it was 5 mGy for those who were exposed at 2.5 km and 2.7 km, respectively. Among LSS members, $\sim 38\,500$ had a weighted absorbed colon dose of <5 mGy, $\sim 30\,000$ had a dose of 5–100 mGy, $\sim 15\,800$ had a dose of 100 mGy to 1 Gy, and ~ 2400 had a dose of 1 Gy or higher [2, 3].

Residual radiation is not taken into account in the individual dose estimates because information on individual exposures to residual radiation is not available. The average external dose estimate from

induced radiation exposure for an individual who spent 12 h at 200 m from the hypocenter during the day following the bombing was ~ 80 mGy in Hiroshima and ~ 18 mGy in Nagasaki. It was <0.5 mGy at 1000 m in both cities. Those doses are estimated to have decreased by half every day [1]. In the areas where radioactive fallout was recorded in early surveys, the average external dose estimate due to exposure to radioactive fallout ranged from 10 to 30 mGy in Hiroshima and from 200 to 400 mGy in Nagasaki [4]. As the number of people exposed in these areas of Nagasaki was small (several hundred) and the risk estimates of disease after exposure to atomic bomb radiation have been estimated primarily from the dose response measured among survivors exposed to 1 Gy or more of direct radiation (discussed later), it is thought that exposure to residual radiation does not notably affect the LSS risk estimates. Some rain that fell shortly after the bombings was stained black by soot and dust from the blast and by smoke from the fires that burned in the cities. This 'black rain' was thought by many to have been polluted with radioactive fallout. However, a recent report indicated no increase in mortality or cancer incidence in LSS members who reported rain exposure shortly after the bombings compared with those reporting no such rain exposure in surveys from 1949 to 1961 [5].

RADIATION-RELATED RISK OF CANCER IN THE LSS

Excess leukemia cases were first noticeable a few years after the bombings and peaked 6–8 years after the bombings. The relative risk was ~ 70 times higher among children exposed at the age of 10, and rapidly decreased with exposure at older ages. For more than five decades, a heightened risk persisted for individuals exposed at earlier ages, though those exposed at age 30 or older had almost no increased risk, even in the earliest period after the bombings. The excess relative risk (ERR) for acute myeloid leukemia showed a non-linear concave increase with dose, while that for acute lymphocytic and chronic myeloid leukemia was mostly linear [6, 7]. In more recent studies, an increased risk of myelodysplastic syndrome has also been observed, showing a linear dose-response [8].

An increased risk of solid cancers has been clear since ~ 10 years after the bombing and persists today. The sex-averaged risk of all solid cancers increases linearly with radiation dose by ~ 40 – 50% per Gy (i.e. $ERR/Gy = 0.4$ to 0.5) for both mortality and incidence at attained age 70 after exposure at age 30. This interpretation is based

Table 1. Free-in-air DS02 dose (kerma) in gray by ground distance from the hypocenter

Ground distance from the hypocenter (m)	Hiroshima			Nagasaki		
	Neutrons	Gamma-rays	Total (10 \times neutrons + gamma-rays)	Neutrons	Gamma-rays	Total (10 \times neutrons + gamma-rays)
1000	0.260	4.22	6.82	0.125	8.62	9.87
1500	0.009	0.527	0.617	0.005	0.983	1.033
1800	0.001	0.165	0.175	0.0008	0.299	0.307
2000	0.0004	0.076	0.080	0.0002	0.138	0.140
2500	<0.0001	0.013	0.013	<0.0001	0.023	0.023

From [DS02 report], weighted total dose was calculated by the author.

primarily on the findings for survivors exposed to 1 Gy or more of atomic bomb radiation (Fig. 2). The risk increases significantly at and above doses of 0.2 Gy. The modeled linear dose-response indicates no threshold; this observation is illustrated by the 0.15 Gy upper limit of the 95% confidence interval, as stated in the latest mortality report [9]. Whether cancer risk increases after radiation exposure varies by organ; risk for cancers of the bladder, female breast, lung, brain, thyroid gland, colon, esophagus, ovary, stomach, liver and skin (excluding melanoma) increases significantly, but that of the pancreas, rectum, uterus, prostate and kidney parenchyma does not.

Since background rates of cancer are generally lower in females than males, the ERR of all solid cancers is higher in women than in men, though the excess absolute rate (EAR) is similar between the two sexes. The ERR is higher in those exposed at younger ages, which implies higher radiosensitivity or vulnerability to radiation in those years. The ERR decreases with attained age, but the EAR increases, which is likely due to an increase in the background rate of cancer with aging. These effect modifiers (i.e. sex, age at exposure, and attained age) play different roles at the various cancer sites [9, 10].

Radiation-related risk has been analyzed and reported for cancers of several sites separately, and some of these analyses have taken lifestyle factors into consideration. Radiation-related risk of lung cancer in moderate smokers was as large as that in heavy smokers, which indicates there is positive interaction between radiation and smoking

among moderate smokers, but not among heavy smokers. This positive interaction was seen in each of the different histological types of lung cancer [11, 12]. In contrast, there was no interaction seen between radiation and smoking for risk of urothelial cancer [13]. Radiation-associated risk of colon cancer was highest in the healthy body mass index (BMI) range, but the difference in risk between the healthy and unhealthy BMI ranges was not significant [14]. Skin cancer showed a linear-threshold dose-response, with a threshold dose of 0.63 Gy; possible interaction was seen between exposure to radiation and exposure to sunlight [15]. Bone sarcoma also showed a threshold dose, but the number of cases was small ($n = 19$) and this result is therefore unreliable. Soft tissue sarcoma showed a linear dose-response [16, 17]. Analysis of thyroid cancer confirmed the previous finding of a relatively higher ERR/Gy compared with that of other site-specific cancers and of a remarkably high ERR/Gy among those exposed and/or diagnosed at young ages [18].

It is difficult to estimate radiation-related risk of disease at low-dose levels. In addition to the weak statistical power that can be expected from the limited effects seen at low-dose levels, there are several other conditions that contribute to the difficulty in generating risk estimates. First, individual dose estimates at low-dose levels are less certain among distal survivors because their detailed shielding conditions were not surveyed and had to be extrapolated. Second, potential exposure to residual radiation as well as cumulative exposure to medical and natural background radiation have the potential to be relatively influential at low-dose levels. As all who were present at the time of the bombings were non-selectively exposed to atomic bomb radiation, confounding was not observed to a great degree in the evaluation of radiation risks on health in the LSS. Yet, among zero-dose survivors, mortality rates were heterogeneous by distance [19]. People who were not in the city at the time of the bombing also had different rates from those zero-dose survivors [10]. These variations in background rate constitute a third challenge in estimating risk at low-dose levels: given that low doses of atomic bomb radiation must be calculated on top of an uncertain background dose, the two values can potentially overlap, becoming indistinguishable. Furthermore, interaction with other risk factors may distort radiation risk estimates in analyses that do not consider these factors. Non-differential distribution of strong risk factors, that is, distribution of strong risk factors that does not change by the strata of radiation dose, widens the confidence intervals of risk estimates. Background rates of cancer mortality and cancer incidence in the LSS have changed over the long observation period. These background changes should not theoretically affect radiation risk estimation, but they may impact statistical power and the magnitude of interaction with other risk factors.

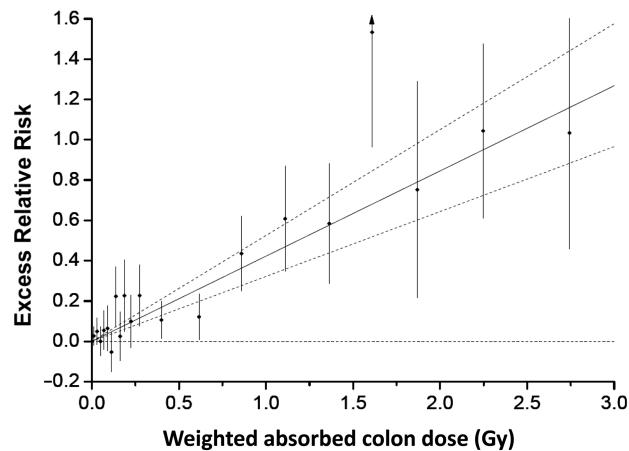


Fig. 2. Dose-response of mortality risk from all solid cancer, LSS, 1950–2003. (Modified from Fig. 4 of Ozasa K, Shimizu Y, Suyama A *et al.* Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res* 2012;177:229–43. This figure is used with the permission of *Radiation Research*.) The solid line is the fitted linear, gender-averaged ERR dose response, and the dashed line is its 95% confidence range. The points are non-parametric estimates of the ERR by dose category and the bars are their 95% confidence intervals. The non-parametric estimates at low-dose levels indicate great uncertainty. This uncertainty is not reflected in the linear dose response or its confidence range because linear fit was estimated in large part by extrapolation from dose levels of 1 Gy or higher.

IN UTERO EXPOSED SURVIVORS AND THE F₁ COHORT

Cancer incidence in survivors exposed prenatally is remarkably similar to incidence among those exposed in early childhood, though observed outcomes have been too few to provide conclusive results [20]. On the other hand, no increased risk of cancer incidence or cancer mortality associated with parental radiation dose has been observed in children of atomic bomb survivors, although these subjects were still relatively young when these results were established, and a longer period of follow-up is necessary [21, 22, 23].

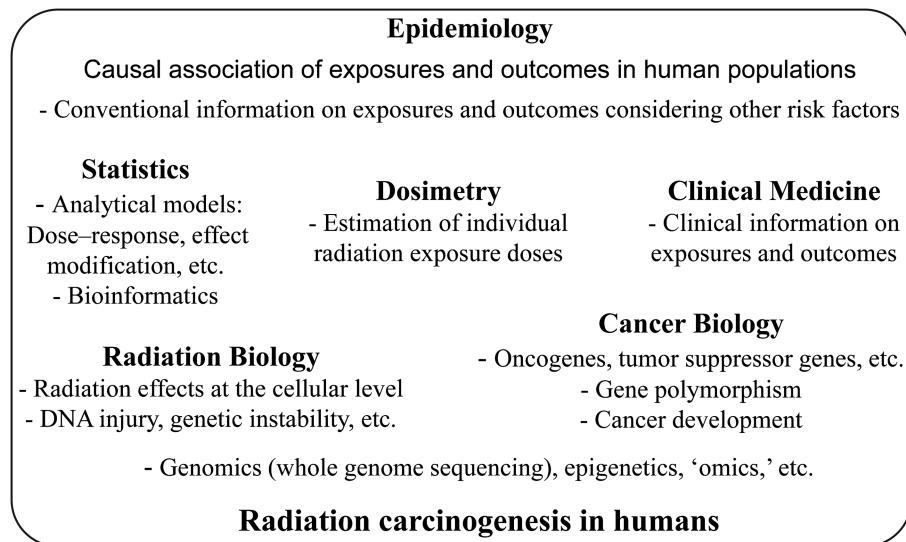


Fig. 3. Epidemiological perspective on radiation-induced cancer.

RADIATION CARCINOGENESIS AND EPIDEMIOLOGY

The purpose of analytical epidemiology is to investigate causal associations between exposures and outcomes in human populations. Analytical epidemiology uses not only conventional information on exposures, but also information obtained from human biosamples in order to study causal associations using biological hypotheses (Fig. 3). Conventional epidemiological findings from the RERF cohorts have given many important clues as to the process of radiation carcinogenesis. The most apparent clues are the differences in both the dose-response relationship and the latency period between leukemia and solid cancers. Another hint arises in the differences seen by sex between the ERR and EAR of radiation on the same cancer site. For example, both the ERR and EAR of all solid cancers reveal a linear association with radiation dose. However, the magnitude of the ERR is quite different between the two sexes, while the EAR is similar between them [9, 10]. This finding has been used to construct the naïve idea that the radiation-related risk of cancer is directly proportional to the absolute number of cells injured by radiation, but that it is independent of baseline cancer rates, which are often quite different between males and females. This pattern, however, has not been consistent across cancer sites. Furthermore, there are similar linear radiation dose-response observations for the ERRs of both first and second primary solid cancers and leukemias, though background incidence rates are higher for second primary solid cancers and leukemias [24]. The similar relative risk of radiation between first and second cancers regardless of their background rates indicates that the relative risk of cancer after radiation exposure is independent of baseline rates, in contrast to the above idea. Current and future investigations, such as the association of tissue stem cell kinetics and variation in cancer risk among different tissues [25], will give important insights into radiation carcinogenesis and the nature of the linear increase in the ERR by dose. Positive or negative interaction between radiation exposure and other risk factors also suggests synergic or competitive actions on carcinogenesis.

Molecular mechanisms have been directly investigated at RERF. Some molecular mechanisms are more frequently observed in cancers that developed in survivors exposed to higher doses of radiation. For example, rearrangements of *RET/PTC* have preferentially occurred in papillary thyroid cancers among the atomic bomb survivors exposed to the highest radiation doses [26, 27]. For gastric cancer, some IL-10 haplotypes have a stronger association with risk of intestinal-type cancer than does radiation exposure, while both these IL-10 haplotypes and radiation greatly increase the risk of diffuse-type cancer. However, negative interaction is seen between these two risk factors [28]. Not only predisposition to radiation-induced cancer defined by polymorphisms on germline genes, but also somatic mutations specific to radiation-induced cancers will need to be investigated using advanced technologies such as whole genome sequencing.

In conclusion, traditional cancer epidemiology has uncovered major aspects of the effects of atomic bomb radiation on health. There are, however, many issues left unsolved, such as the effects of atomic bomb radiation on survivors who were exposed at very young ages and *in utero*, the potential genetic effects on the children of survivors, and the effects of exposure to low-dose levels of radiation. Furthermore, there is need to investigate the impact of confounding and effect modification. The uncertainty of individual radiation dose estimates and possible additional radiation exposures should also be duly considered. Studies on radiation carcinogenesis in RERF cohorts with epidemiological designs will be conducted in collaboration with pathologists, cancer biologists and radiation biologists.

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