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Review

Long-term follow-up of atomic bomb survivors

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ABSTRACT

The Life Span Study (LSS) is a follow-up study of atomic bomb (A-bomb) survivors to investigate the radiation effects on human health and has collected data for over 60 years. The LSS cohort consists of 93,741 A-bomb survivors and another 26,580 age and sex-matched subjects who were not in either city at the time of the bombing. Radiation doses have been computed based on individual location and shielding status at the time of the bombings. Age at death and cause of death are gathered through the Japanese national family registry system and cancer incidence data have been collected through the Hiroshima and Nagasaki cancer registries. Noncancer disease incidence and health information are collected through biannual medical examinations among a subset of the LSS. Radiation significantly increases the risks of death (22% at 1 Gy), cancer incidence (47% at 1 Gy), death due to leukemia (310% at 1 Gy), as well as the incidence of several noncancer diseases (e.g. thyroid nodules, chronic liver disease and cirrhosis, uterine myoma, and hypertension). Significant effects on maturity (e.g. growth reduction and early menopause) were also observed. Long-term follow-up studies of the A-bomb survivors have provided reliable information on health risks for the survivors and form the basis for radiation protection standards for workers and the public.

Contents

1. Introduction

Interest in the effects of radiation on human health has increased since the Fukushima Daiichi nuclear disaster. Much has been learned from the first experience of large-scale human ionizing radiation exposures, the atomic bombs (A-bomb), which were dropped on Hiroshima and Nagasaki in August 1945. Both cities were completely devastated. The exact number who perished is unclear because of the chaotic conditions after the bombings, but about 140,000 people in Hiroshima and 70,000 people in Nagasaki were estimated to have died. Many survivors were injured and suffered acute radiation symptoms such as bleeding and epilation. However, at the time, it was unclear whether the survivors would suffer long-term health effects. The Radiation Effects Research

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Foundation (RERF) and its predecessor, the Atomic Bomb Casualty Commission (ABCC), have conducted long-term follow-up studies of the A-bomb survivors. The results from these studies provide reliable information on health risks for the A-bomb survivors and are the basis for radiation protection standards for radiation workers and the public. In this review, we will introduce the long-term A-bomb survivors' follow-up studies and their results.

2. Subjects and primary outcomes

The ABCC was established to explore the health effects among the A-bomb survivors in Hiroshima and Nagasaki by the US National Academy of Sciences in 1947. In the early years after the bombing, physicians noticed an increase in leukemia patients in Hiroshima and Nagasaki. During the first decade of the ABCC, studies on A-bomb survivors were diverse and designed on an ad hoc basis with each investigator establishing his own study population [1]. Carefully designed epidemiological follow-up studies that systematically catalogued the health of the A-bomb survivors were required [2,3]. A comprehensive review of ABCC's work was performed in 1955 (The Francis Committee) and recommended extensive revisions to the design of the research studies. In response to the recommendations of the Francis Committee, the ABCC established the Life Span Study (LSS) cohort based on data obtained from the A-bomb survivor's survey, which was an addendum to the 1950 Japanese national census. Survivors who still resided in either city in 1950 and who were exposed within 2.5 km of the A-bombs were included in the cohort. Two sets of sex- and age-matched residents were also sampled. The first set was exposed between 2.5 km and 10 km and the second were not in either city at the time of bombing. The full LSS cohort consists of 120,321 persons; 93,741 A-bomb survivors and another 26,580 subjects who were not in either city at the time of the bombing. The LSS features a broad range of ages at the time of bombing as well as both sexes. The epidemiological follow-up was retrospective between 1950 and 1958, and prospective beyond 1958. The RERF was established in 1975 as the successor organization to the ABCC and has continued the studies until the present. Primary outcomes of the LSS are age at death and cause of death, which are gathered through the Japanese national family registry system, and cancer incidence using data collected by the Hiroshima and Nagasaki cancer registries established in 1958. About 20,000 of the original LSS cohort were also invited to participate in biennial medical examinations as subjects of the Adult Health Study (AHS). Noncancer disease incidence and health information are collected through the medical examinations.

3. Radiation dose estimates and other collected information

Radiation doses for 15 specific organs have been computed based on an individual's location and shielding status at the time of the bombings in terms of γ-ray and neutron radiation dose based on physical and theoretical calculations. Detailed information regarding location and shielding status was obtained from more than 20,000 survivors who were within 1.6 km of the hypocenter in Hiroshima and 2 km in Nagasaki. Less-detailed shielding information is available for remaining subjects. Dosimetry Systems have been updated several times over the years; the latest system was created in 2002 (Dosimetry System 2002, DS02) [4]. Data on other factors that may confound or interact with radiation risk estimates, such as lifestyle habits (smoking, drinking, etc.), medical radiation exposure, and socioeconomic status have been collected via a series of questionnaires mailed periodically on five occasions to the LSS subjects.

4. Results

4.1. Mortality risks (cancer and noncancer)

Radiation risk estimates of mortality among the LSS have been reported periodically. The latest report was based on mortality follow-up data between 1950 and 2003 [5]. About half of the subjects who were in their 20 s at the time of bombing were alive at that time while nearly all who were over the age of 50 at the time of bombing have died. Radiation risks were determined using excess relative risk (ERR) and excess absolute risks (EAR) models. ERR is defined as relative risk-1.

The sex-averaged ERR per gray for total deaths was statistically significant, 0.22 (95% confidence interval (CI): 0.18, 0.26). The ERR was 0.42 (95%CI: 0.32, 0.53) for solid cancer mortality at an attained age of 70 years after exposure to 1 gray at age 30 (i.e., a 42% increase at 1 gray). One gray of radiation is a substantial dose, possibly resulting in acute symptoms; it is approximately 300 times greater than the average yearly background radiation dose of US residents. The relationship between radiation dose and mortality risk due to all solid cancer was well described by a linear model. For all solid cancer, the EAR was 26.4 excess deaths per 10,000 person-years·Gy. The ERR in females was around twice as high as that in males, while a sex difference in EAR was not observed (female/male of EAR = 1.1). Both ERR and EAR were significantly modified by age at exposure and attained age. The ERR/Gy declined with increasing age at exposure as well as attained age. The EAR significantly declined with age at exposure and increased with attained age.

Deaths due to many types of cancer, including those of the stomach, colon, liver, lung, female breast, etc., showed significantly elevated risks (Fig. 1). Cancers of the rectum, pancreas, uterus and other less common tumor sites showed positive but non-significant risk estimates. Significant excess risk was also observed for leukemia. A linear-quadratic model with upward curvature provided the best fit for leukemia risk. The sex-averaged ERR of death due to leukemia was 3.1 (95%CI: 1.8, 4.3) at 1 Gy and 0.15 (95%CI: −0.01, 0.31) at 0.1 Gy.

Significant elevated risks were also observed for non-neoplastic diseases of the blood, circulatory system and respiratory system. Shimizu et al. investigated the radiation risk of mortality from heart disease and stroke [6]. The ERR per Gy was 9% (95%CI: 1, 17%) for stroke and 14% (95%CI: 6, 23%) for all heart disease. Adjustments for smoking, alcohol intake, education, type of occupation, obesity and diabetes produced inconsequential changes in the ERR per gray.

4.2. Cancer incidence

Cancer incidence reports have also been periodically generated. Recent estimates were published for cancer incidence in 2007 [7]. Among 105,427 eligible LSS cohort members with DS02 dose estimates who had not died or been diagnosed with cancer before 1958, 17,448 first primary solid cancers were diagnosed during 1958–1998. The most common cancer was stomach cancer (27%) followed by cancers of lung (10%), liver (9%), colon (9%), female breast (6%) and cervix (5%). The distribution of cancers by site was similar to what would be expected in Japan for the same period. A linear dose–response best fit the incidence data for solid cancer. Generally, the risk estimates for all solid cancer incidence were similar to all solid cancer deaths. Radiation risk estimates differed by organ site, while significant excess risks were obtained for many of the major types of solid cancers, including stomach, lung, liver, colon, female breast, ovary, bladder, thyroid, and skin (Table 1). ERR estimates for most types of cancer were positive, although not always statistically significant leading to the general conclusion that radiation exposure appears to be associated with an increased risk for all cancers.

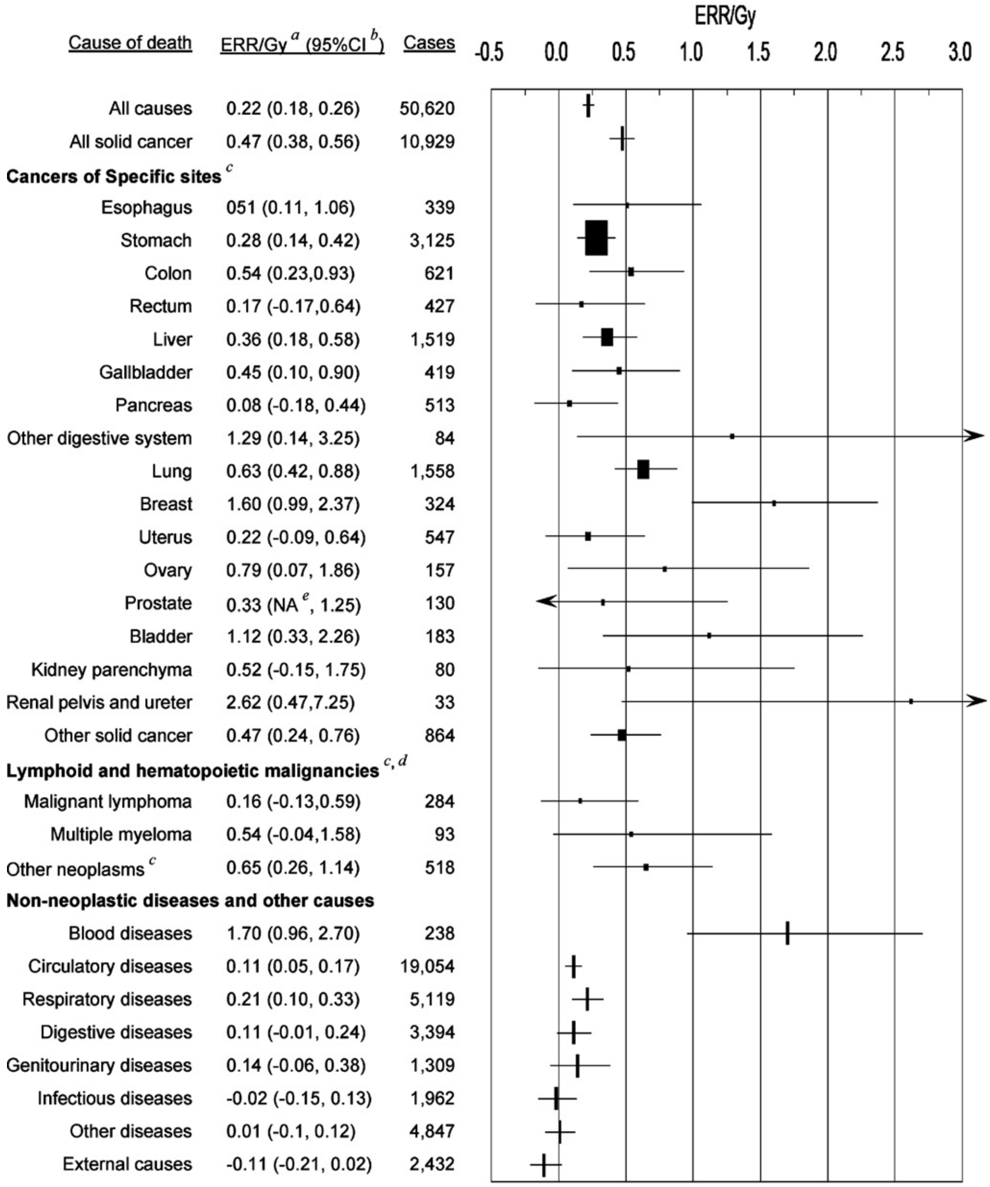

Fig. 1. Estimates of excess relative risk (ERR) per Gy and 95% confidence interval (CI) for major causes of death. From: Ref. [5]. [a]ERR was estimated using the linear dose model, in which city, sex, age at exposure, and attained age were included in the background rates, but not allowing radiation effect modification by those factors. [b]Confidence interval. Horizontal bars show 95% confidence intervals. [c]The size of plots for site-specific cancers was proportional to the number of cases. [d]ERR (95%CI) of leukemia was 3.1 (1.8, 4.3) at 1 Gy and 0.15 (−0.01, 0.31) at 0.1 Gy based on a linear-quadratic model with 318 cases (not displayed in the figure). [e]The lower limit of 95% CI was lower than zero, but not specified by calculation.

An increase of leukemia incidence was the earliest (non-acute) effect observed among the A-bomb survivors. A registry of leukemia and related disorders was established around 1950 in Hiroshima and Nagasaki [8]. Estimating the risk of incidence of leukemia was therefore possible starting with follow-up from 1950. The dose–response for leukemia appears to be non-linear and rises as dose and dose-squared with similar estimates as those observed for mortality.

4.3. Morbidity

The relationship between radiation dose and the incidence of noncancer diseases has been examined using data from the AHS participants. The latest report using longitudinal data between 1958 and 1998 detected a significantly positive dose response for thyroid nodules (the relative risk at 1 Gy ($RR_{1\,Gy}$) = 1.33, 95%CI: 1.19, 1.49), chronic liver disease and cirrhosis ($RR_{1\,Gy}$ = 1.15, 95%CI: 1.15, 1.25), uterine myoma ($RR_{1\,Gy}$ = 1.46, 95%CI: 1.27, 1.67), hypertension ($RR_{1\,Gy}$ = 1.03, 95%CI: 1.00, 1.06), and myocardial infarction among survivors less than 40 years at the time of bombing ($RR_{1\,Gy}$ = 1.25, 95%CI: 1.00, 1.69) and calculus of the kidney and ureter for men ($RR_{1\,Gy}$ = 1.47, 95%CI: 1.13, 1.96) [9].

Significant associations between radiation dose and the prevalence of hypertension [10], elevated serum cholesterol concentration [11], aortic arch calcification [12] and post operative cataract [13] were reported. Late radiation effects have also been found in biomarkers of inflammation [14–16], deficient immunological responses [17], and alterations in the immune cell repertoire [18,19].

Table 1
Site-specific gender-averaged excess relative risk and excess absolute rate for incidence of selected sites and all solid cancers.

Site	Excess relative risk[a]	Excess absolute rate[b]
All solid	0.47 (0.40; 0.54)[c]	52 (43; 60)
Stomach	0.34 (0.22; 0.47)	9.5 (6.1; 14)
Colon	0.54 (0.30; 0.81)	8.0 (4.4; 12)
Liver	0.30 (0.11; 0.55)	4.3 (0.0; 7.2)
Lung	0.81 (0.56; 1.1)	7.5 (5.1; 10)
Non-melanoma skin	0.17 (0.003; 0.55)	0.35 (0.03; 1.1)
Female breast	0.87 (0.55; 1.3)	9.2 (6.8; 12)
Ovary	0.61 (0.00; 1.5)	0.56 (0.02; 1.3)
Bladder	1.23 (0.59; 2.1)	3.2 (1.1; 5.4)
Brain, CNS[d]	0.62 (0.21; 1.2)	0.51 (0.17; 0.95)
Thyroid	1.21 (0.43; 2.9)	1.2 (0.5; 2.2)

Adapted from Table 11 in Ref. [7].
[a] Estimated gender-averaged excess relative risk at 1 Gy for attained age 70 after exposure at age 30.
[b] Estimated gender-averaged excess absolute rate at 1 Gy for attained age 70 after exposure at age 30 with units of excess cases per 10,000 PY Gy.
[c] 90% confidence intervals.
[d] Central nervous system.

4.4. Growth

The radiation effect on growth was studied among AHS participants who were under 10 years old at the time of bombing and had at least three height and weight measurement at ages 19–27 years old [20]. A significant growth reduction due to exposure to A-bomb radiation was observed. The mean values of height and weight by radiation dose, using parameter estimates based on a multiplicative growth-curve model were calculated. The differences of expected values for those exposed at 2.0 Gy were −1.6 cm for height and −1.5 kg for weight. In another study using a broader range of age at the time of the bombing, a reduction of stature related to radiation dose was observed only for subjects who were less than 19 years of age at the bombing (95%CI: 17, 21 years) [21]. The effect peaked for those aged 5–15 years the age at the bombing.

4.5. Gynecological effects of radiation

Several investigations of a possible association between radiation exposure and age at menarche have been conducted but most have reported non-significant results [22–26]. In a study of girls who visited ABCC in Hiroshima for periodic examination between 1949 and 54, the mean age of menarche among those who experienced the bomb within 2 km of the hypocenter ($N = 1007$) was 14.71 while for 993 girls who did not experience the A-bomb, the age was about the same age [24]. There were no significant differences based on comparisons with distances from the hypocenter or whether epilation was experienced [25,26].

The frequency of menstrual disorders (amenorrhea) was increased among female A-bomb survivors who were exposed closer to the hypocenter in Hiroshima in an investigation conducted immediately after the bombing [27]. Among 880 women who visited ABCC in Hiroshima for periodic examinations between 1949 and 54, about half experienced amenorrhea and that percentage was higher among women with acute symptom (69.0%) compared with women without acute symptom (33.7%) [24].

A comparison of age at menopause using the same subjects indicated that the mean age of menopause was lowest among those who experienced acute symptoms after exposure with a mean age at menopause of 45.9 years. For women who were exposed but did not experience acute symptoms, the mean age was 48.55 years, and it was 49.3 years for unexposed women [24]. However, since this study was conducted before all of the women had experienced menopause and at a time when physical injuries and/or psychological effects may still have played a major role, conclusions regarding the direct effects of radiation exposure are tenuous. A more recent study investigating the age at menopause among female LSS subjects using age at menopause obtained from mail surveys indicated a decrease of age at menopause with increased radiation doses for menopause occurring at least 5 years after the exposure [28]. The dose–response curve for EAR and weighted ovarian dose was described best by a linear threshold model with a threshold of 0.40 Gy (95%CI: 0.13, 0.62). Statistical modeling estimated that 37% of women unexposed to radiation experienced menopause prior to age 50 while 44% of women exposed to 1 Gy experienced menopause prior to age 50.

Grant et al. observed that levels of cancer-related hormones and proteins changed with radiation dose in cancer-free AHS females [29]. Serum levels of total estradiol, bioavailable estradiol, testosterone, progesterone, prolactin, insulin-like growth factor-1, insulin-like factor-binding protein 3, and ferritin were measured. Total estradiol and bioavailable estradiol showed a significant decrease with radiation dose in the premenopausal period and a significant increase with radiation dose in the postmenopausal period.

Wong et al. noted an increased incidence of uterine myoma in AHS subjects [30]. Ultrasound examinations were performed on AHS females between 1991 and 1993. Among 1190 females who received an ultrasound examination and whose uterus was visualized, 236 were found to have uterine nodules. A significant dose–response relationship between the prevalence of uterine nodules and uterine doses was observed (odds ratio at 1 Gy = 1.61, 95%CI: 1.12, 2.31).

5. Conclusions

The LSS cohort was carefully designed and continues to be followed to this day. Individual doses were estimated based on location and shielding status at the time of the bombing based on interviews. Nearly complete mortality data for 120,000 subjects have been continuously collected for over 60 years. Radiation effects on cancer incidence can be estimated using data from the Hiroshima and Nagasaki cancer registries, which were the first cancer registries established in all of Japan. Cancer incidence data is an important addition as it allows investigations of several types of cancers with good prognoses (e.g. thyroid cancer and female breast cancer) or that have markedly improved survival rates due to screening efforts (e.g. stomach cancer and colon cancer). Incidence of noncancer diseases and other health information are collected thorough biannual examinations of the AHS cohort, which is a subgroup of the LSS. As the LSS includes both sexes and a broad range of ages at the time of the bombings, it is possible to examine the modification of radiation risks by sex and age. Long-term follow-up studies of the A-bomb survivors have revealed that radiation exposure increases the risk of cancer in almost all sites and that this increase lasts throughout the lifetime of the survivors. Radiation also increases the incidence and/or mortality of diseases other than cancer. In the future, we hope to clarify the effects of low-dose exposure and uncover more about the mechanisms by which radiation increases the risks of different diseases. In this short review, we have only discussed the LSS and AHS cohorts. RERF also follows 3600 survivors who were exposed in utero [31,32] and 76,000 persons conceived after the bombing to parents exposed to A-bomb radiation [33,34]. Additional information and downloadable data are available at RERF's website: http://www.rerf.or.jp.

Contributors

Paper review and drafting of manuscript was performed by RS. Critical revisions and editing were conducted by EG and KO.

Competing interests

The authors have nothing to disclose.

Provenance and peer review

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