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REGULAR ARTICLE

Cancer mortality among atomic bomb survivors exposed as children

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Abstract
Objectives To compare cancer mortality among A-bomb survivors exposed as children with cancer mortality among an unexposed control group (the entire population of Japan, JPCG).
Methods The subjects were the Hiroshima and Nagasaki A-bomb survivor groups (0–14 years of age in 1945) reported in life span study report 12 (follow-up years were from 1950 to 1990), and a control group consisting of the JPCG. We estimated the expected number of deaths due to all causes and cancers of various causes among the exposed survivors who died in the follow-up interval, if they had died with the same mortality as the JPCG (0–14 years of age in 1945). We calculated the standardized mortality ratio (SMR) of A-bomb survivors in comparison with the JPCG.
Results SMRs were significantly higher in exposed boys overall for all deaths, all cancers, leukemia, and liver cancer, and for exposed girls overall for all cancers, solid cancers, liver cancer, and breast cancer. In boys, SMRs were significantly higher for all deaths and liver cancer even in those exposed to very low doses, and for all cancers, solid cancers, and liver cancer in those exposed to low doses. In girls, SMRs were significantly higher for liver cancer and uterine cancer in those exposed to low doses, and for leukemia, solid cancers, stomach cancer, and breast cancer in those exposed to high doses.
Conclusions We calculated the SMRs for the A-bomb survivors versus JPCG in childhood and compared them with a true non-exposed group. A notable result was that SMRs in boys exposed to low doses were significantly higher for solid cancer.

Keywords Atomic bomb · Cancer · Children · Radiation · SMR

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Introduction

Several recent studies have proposed environmental factors, infections, genetic disorders, and ionizing radiation as risk factors for childhood cancer [1, 2]. Today, more than 60 years since the atomic bombings, the Radiation Effects Research Foundation (RERF) continues to publish works on the effects of radiation on the health of A-bomb survivors, especially the incidence of and mortality from cancer [3, 4]. To investigate the cancer risks for the exposed survivors of the Hiroshima bombing examined in the life span study (LSS) report 12 by RERF, Watanabe et al. [5] calculated the standardized mortality ratio (SMR) based on data from LSS report 12. Their results showed that A-bomb

survivors aged 0–34 years at the time of the bombing, even those exposed to very low primary radiation doses, had a high SMR due to various cancers in comparison with genuine non-exposed controls.

However, current epidemiological knowledge on radiation risks in children is poorer than that of adults, because fewer and smaller study populations, especially those exposed to low doses of ionizing radiation, have been investigated [6, 7]. The cancer risk in children after postnatal diagnostic irradiation has also been studied less extensively [8–11]. Among those studies that have been done, the potential risks of diagnostic uses of ionizing radiation such as X-rays in children were reported by Stewart et al. [12]. From the results of many case–control studies and estimates of excess absolute risk (EAR), Doll and Wakeford [13] supported the association reported by Stewart et al. On the other hand, Hammer et al. [11] reported no increase in the risk of childhood cancer for about 100,000 children who had been examined using diagnostic X-rays. This uncertainty in studies of cohorts exposed to radiation in childhood has resulted in continuing controversy regarding the causal interpretation of the association between radiation exposure in children and cancer [14].

From the standpoint of child health, based on LSS report 12, we consider the SMRs for cancer among A-bomb survivors aged 0–14 at the time of the bombing by comparing them with a control group consisting of the entire population of Japan (JPCG). These subjects were school age, ranging from 5 to 19 years old when the LSS was started in 1950, and studied until 40 years later when they were 45–59 years of age in 1990 (45 years after the bombing).

Materials and methods

We evaluated the SMRs for cancer deaths among young children at the time of the bombings, based on the method used in the report by Watanabe et al. [5]. The subjects in the present study were the Hiroshima and Nagasaki group (LSS group) reported in LSS report 12, and a control group consisting of JPCG. We used JPCG as a control group instead of residents in prefectures neighboring Hiroshima and Nagasaki (e.g., Okayama and Saga), because the pre-1971 mortality data for these prefectures were not available to us and, therefore, we could not adequately follow any childhood cohort from these prefectures as a control group. We did not use data from the latest LSS report, report 13, because the disease categories were changed, e.g., "leukemia" became "all hematopoietic cancers," making linkage with our data difficult.

Data for both the LSS group and the control group were collected and categorized by sex and age at the time of the bombing (in 5-year age groups) to calculate the SMR. We used the number of cause-specific deaths and population for each age group obtained from vital statistics and population censuses [15–19]. We took the years 1950–1990 (divided into 11 intervals) as the follow-up interval for LSS report 12 and as the observation period for the present study. The subjects in this study, therefore, were people we could follow during the years 1950–1990, who were 0–14 years old in 1945 (the number of people in the JPCG aged 0–14 years in 1945 was about 13,540,000 males and 13,250,000 females in 1950 [15–17]. The number of people in the LSS group is shown in Table 1).

Using the data on exposed survivors from LSS report 12, we initially calculated the observed person-years, as well as the observed number of deaths (O), according to follow-up interval, sex, age at exposure (0–14 years old), colon radiation dose (3 levels: described in detail later in this report), and cause of death. We then calculated the mortality rate by cause of death in the JPCG, according to follow-up interval, sex, and age in 1945 (in 5-year age groups). The expected number of deaths (E) was calculated for each category (sex, age at exposure, colon radiation dose, and cause of death) of the LSS group, using an indirect method based on observed person-years. These O and E values were then used to calculate SMR ($=O/E$). If the SMR is higher than 1.0, then A-bomb survivors aged 10–14 at the time of the bombing had higher mortality rates in the years 1950–1990 than did a comparison group taken from age and following year matched national mortality data. The statistical significance of the SMR was analyzed using the chi-square test. We also estimated the 95% confidence interval (CI) for the SMRs using the formula of Watanabe et al. [5].

In the present study, the colon radiation dose (Sv) was divided into three categories: under 0.005 (very low dose, VLD), from 0.005 to <0.1 (low dose, LD), and from 0.1 to <4.0 (high dose, HD), respectively. This colon radiation dose was the estimated radiation dose

Table 1 Number of subjects in LSS group aged 0–14 at time of bombing, by sex, colon radiation dose, and city in 1950

City	Sex	Dose categories (Sv)			
		<0.005 (very low)	0.005 to <0.1 (low)	≥0.1 (high)	Total
Hiroshima	Male	2,940	3,707	1,658	8,305
	Female	2,814	3,334	1,788	7,936
Nagasaki	Male	2,874	1,784	638	5,296
	Female	2,729	1,842	711	5,282
Total	Male	5,814	5,491	2,296	13,601
	Female	5,543	5,176	2,499	13,218

Table 2 Standardized mortality ratio of LSS group compared with JPCG for selected cancers

Cause of death	Male				Female			
	O^a	E^b	SMR[c] (95% CI)	p value[d]	O^a	E^b	SMR[c] (95% CI)	p value[d]
All deaths	1,456	1,282.5	1.135 (1.078–1.194)	<0.001	761	714.5	1.065 (0.992–1.142)	0.085
All cancers	331	252.0	1.313 (1.179–1.459)	<0.001	246	204.5	1.203 (1.062–1.358)	0.004
Leukemia	34	17.7	1.916 (1.374–2.612)	<0.001	17	12.6	1.346 (0.844–2.057)	0.277
Solid cancers	284	223.6	1.270 (1.131–1.422)	<0.001	221	185.8	1.190 (1.043–1.352)	0.011
Stomach	74	74.9	0.988 (0.788–1.225)	0.962	59	57.4	1.028 (0.797–1.306)	0.887
Colon	15	12.8	1.176 (0.717–1.842)	0.625	8	11.0	0.728 (0.374–1.312)	0.452
Liver	89	37.1	2.399 (1.951–2.922)	<0.001	14	5.9	2.384 (1.430–3.786)	0.002
Lung	27	25.2	1.070 (0.737–1.510)	0.801	13	11.7	1.107 (0.652–1.785)	0.825
Female breast	–	–	–	–	44	26.6	1.651 (1.232–2.174)	0.001
Uterus	–	–	–	–	20	13.9	1.438 (0.935–2.134)	0.134

Data refer to Hiroshima and Nagasaki, both sexes, aged 0–14 at time of bombing, 1950–1990 (total)

[a] Observed number of deaths

[b] Expected number of deaths

[c] Risk among Hiroshima and Nagasaki survivors in LSS relative to Japanese people

[d] Chi-square test

Table 3 Standardized mortality ratio of LSS group compared with JPCG for selected cancers

Cause of death	Male				Female			
	O^a	E^b	SMR[c] (95% CI)	p value[d]	O^a	E^b	SMR[c] (95% CI)	p value[d]
All deaths	645	554.8	1.162 (1.076–1.254)	<0.001	310	301.3	1.029 (0.921–1.147)	0.635
All cancers	129	109.7	1.176 (0.991–1.388)	0.072	85	86.4	0.984 (0.796–1.204)	0.925
Leukemia	8	7.6	1.053 (0.541–1.897)	0.971	3	5.3	0.565 (0.205–1.361)	0.433
Solid cancers	113	97.4	1.160 (0.965–1.384)	0.126	79	78.5	1.007 (0.808–1.240)	0.999
Stomach	28	32.6	0.859 (0.596–1.205)	0.471	20	24.2	0.825 (0.536–1.224)	0.448
Colon	5	5.5	0.903 (0.398–1.850)	0.988	4	4.6	0.861 (0.350–1.888)	0.947
Liver	39	16.3	2.400 (1.759–3.210)	<0.001	7	2.5	2.809 (1.386–5.241)	0.011
Lung	14	11.0	1.272 (0.763–2.020)	0.453	5	5.0	1.007 (0.443–2.062)	0.834
Female breast	–	–	–	–	13	11.2	1.156 (0.681–1.864)	0.708
Uterus	–	–	–	–	7	5.9	1.188 (0.586–2.217)	0.802

Data refer to Hiroshima and Nagasaki, both sexes, aged 0–14 at time of bombing, 1950–1990 (VLD group)

[a] Observed number of deaths

[b] Expected number of deaths

[c] Risk among Hiroshima and Nagasaki survivors in LSS relative to Japanese people

[d] Chi-square test

considering the distance from the hypocenter and the radiation shielding provided by buildings based on DS86 [20]. (DS86 is nearly equivalent to DS02, the newest dose estimation system, but both look only at the initial radiation and do not take into account residual radiation and radioactive fallout.) Deaths were categorized as all deaths, and deaths from all cancers, leukemia, solid cancers, stomach cancer, colon cancer, liver cancer, lung cancer, female breast cancer, and uterine cancer. This study aimed to compare people exposed to each dose category (VLD, LD, or HD group) with JPCG as the reference population.

Results

For all deaths and deaths due to selected cancers, the SMRs of Hiroshima and Nagasaki atomic bomb survivors exposed in childhood (LSS group) are shown in comparison with the JPCG as the reference population in Tables 2, 3, 4, and 5.

SMR of death for total LSS group in comparison with JPCG (Table 2)

For all deaths and all cancers, the respective SMRs for males were shown to be significantly high. By cancer site,

Table 4 Standardized mortality ratio of LSS group compared with JPCG for selected cancers

Cause of death	Male				Female			
	O^a	E^b	SMR[c] (95% CI)	p value[d]	O^a	E^b	SMR[c] (95% CI)	p value[d]
All deaths	555	517.1	1.073 (0.988–1.164)	0.100	264	276.9	0.953 (0.845–1.072)	0.456
All cancers	127	101.5	1.251 (1.052–1.478)	0.013	80	79.1	1.011 (0.813–1.245)	0.964
Leukemia	5	7.2	0.696 (0.307–1.426)	0.530	3	4.9	0.607 (0.220–1.461)	0.516
Solid cancers	118	90.0	1.311 (1.095–1.558)	0.004	73	71.8	1.017 (0.809–1.263)	0.933
Stomach	32	30.1	1.061 (0.753–1.460)	0.805	20	22.2	0.899 (0.584–1.334)	0.711
Colon	8	5.1	1.556 (0.801–2.806)	0.298	2	4.2	0.471 (0.146–1.312)	0.397
Liver	37	14.9	2.479 (1.802–3.340)	<0.001	6	2.2	2.674 (1.254–5.201)	0.030
Lung	8	10.2	0.787 (0.405–1.419)	0.602	5	4.5	1.104 (0.486–2.261)	0.989
Female breast	–	–	–	–	10	10.3	0.968 (0.531–1.653)	0.959
Uterus	–	–	–	–	11	5.3	2.063 (1.163–3.450)	0.025

Data refer to Hiroshima and Nagasaki, both sexes, aged 0–14 at time of bombing, 1950–1990 (LD group)

[a] Observed number of deaths

[b] Expected number of deaths

[c] Risk among Hiroshima and Nagasaki survivors in LSS relative to Japanese people

[d] Chi-square test

Table 5 Standardized mortality ratio of LSS group compared with JPCG for selected cancers

Cause of death	Male				Female			
	O^a	E^b	SMR[c] (95% CI)	p value[d]	O^a	E^b	SMR[c] (95% CI)	p value[d]
All deaths	256	210.5	1.216 (1.076–1.370)	0.002	187	136.3	1.372 (1.189–1.576)	<0.001
All cancers	75	40.9	1.835 (1.465–2.273)	<0.001	81	39.0	2.075 (1.670–2.550)	<0.001
Leukemia	21	3.0	7.097 (4.660–10.439)	<0.001	11	2.4	4.619 (2.604–7.723)	<0.001
Solid cancers	53	36.2	1.466 (1.122–1.886)	0.007	69	35.5	1.944 (1.537–2.429)	<0.001
Stomach	14	12.1	1.152 (0.691–1.830)	0.698	19	10.9	1.737 (1.117–2.600)	0.022
Colon	2	2.1	0.963 (0.298–2.683)	0.769	2	2.1	0.952 (0.295–2.653)	0.783
Liver	13	5.9	2.193 (1.291–3.537)	0.007	1	1.1	0.880 (0.213–3.245)	0.733
Lung	5	4.1	1.230 (0.542–2.519)	0.829	3	2.2	1.335 (0.485–3.214)	0.866
Female breast	–	–	–	–	21	5.1	4.145 (2.721–6.096)	<0.001
Uterus	–	–	–	–	2	2.7	0.745 (0.230–2.075)	0.910

Data refer to Hiroshima and Nagasaki, both sexes, aged 0–14 at time of bombing, 1950–1990 (HD group)

[a] Observed number of deaths

[b] Expected number of deaths

[c] Risk among Hiroshima and Nagasaki survivors in LSS relative to Japanese people

[d] Chi-square test

SMRs for death due to liver cancer, leukemia, and solid cancer were significantly high. The SMR for female deaths due to all causes did not show a significant difference, whereas the SMR for all cancers was significantly high. By site of cancer, SMRs for deaths due to liver, female breast, and solid cancers were significantly high. The uterine cancer SMR was relatively high, but the difference was not significant.

SMR of death for LSS group in VLD group in comparison with JPCG (Table 3)

The SMR for all deaths in males was significantly high, whereas SMR due to all cancers did not show a significant difference. The SMR for liver cancer among males was significantly high. For other cancers, SMRs for leukemia, solid cancer, and lung cancer were each over 1.0, but they

did not show any significant differences. The SMR for all deaths was not high, and there was no significant difference in SMR for all cancers in females. By site of cancer, the SMR for liver cancer among females was significantly high, whereas SMRs for cancers peculiar to females (such as female breast and uterine cancer) were not high.

SMR of death for LSS group in LD group in comparison with JPCG (Table 4)

The SMR for all deaths among males did not show a significant difference, whereas SMR for all cancers was significantly high. For liver and solid cancer, the respective SMRs for males were shown to be significantly high. In females, there were no significant differences in SMRs for all deaths and all cancers. By site of cancer, SMRs for liver and uterine cancer were significantly high among females.

SMR of death for LSS group in HD group in comparison with JPCG (Table 5)

The SMR in males was significantly high for all deaths and deaths from all cancers. By site of cancer, SMRs for deaths due to leukemia, liver cancer, and solid cancer were significantly high. In females, SMRs for all deaths and all cancers were significantly higher. SMRs for deaths due to leukemia, solid cancer, stomach cancer, and female breast cancer were significantly high. SMRs for leukemia and female breast cancer were especially high.

Discussion

In this study, we calculated the SMRs for all causes of death and various types of cancer by comparing the actual number of deaths among the LSS group with the expected number of deaths during the follow-up period, among the cohort aged 0–14 years in 1945 in JPCG. We found that the SMRs of male survivors exposed to A-bomb radiation were significantly high for all deaths, all cancers, leukemia, solid and liver cancer. The SMRs of female A-bombs survivors were significantly high for all cancers, solid, liver, and female breast cancer. By exposure level, SMRs among males were significantly high for all deaths and liver cancer in the very low category, for all cancers, solid and liver cancer in the low dose category, and for all deaths, all cancers, leukemia, solid and liver cancer in the high dose category. Female SMRs were significantly high for liver and uterine cancer in the very low and low category, and for all deaths, all cancers, leukemia, solid, stomach, and female breast cancer in the high dose category.

The number of deaths in subjects registered as A-bomb survivors in this study was small, because this cohort was in childhood at the time of the bombing. Therefore, it is possible that there were several causes of death in which no significant differences were seen. A study reported by Preston et al. [4] is one of a number of cohort studies of early childhood exposure with long-term, continuous active follow-up. It provided evidence that exposure to radiation in early childhood is associated with increased risks of adult-onset solid cancers in A-bomb survivors. Data by Hammer et al. [11] suggested that the leukemia mortality risk from in utero exposure actually may be lower than risk from childhood exposure. Cancer mortality to age 49 was examined among residents near the Techa River who were exposed to radiation in utero and/or postnatally before the age of 5 [21]. In that study, excess relative risk for solid cancer was not statistically significant. In addition, a strong association between the combined prenatal and postnatal bone marrow dose and leukemia incidence was found, although these factors did not show a significant relationship.

The level of exposure to radiation in the LSS reports was defined as the primary radiation according to DS86 and DS02 only, without taking residual radiation into account. These analyses reported by RERF had some problems: (1) LSS did not investigate the residual radiation value in each subject who had been exposed to the A-bomb, and (2) showed the results for A-bomb survivors in comparison with a non-zero exposed group as an unexposed group [20]. The LSS report, therefore, may have calculated the background risk as higher than it actually was [5, 22]. We estimated SMRs compared with a genuine non-exposed control group by using the Japanese population. When making comparisons across populations with different age–sex distributions, comparisons of each exposure category's SMR to assess the dose–response trend are usually not fully standardized [23]. We therefore estimated SMRs between each dose group and JPCG. However, because the three dose category groups in this study had similar age–sex distributions (Table 6), SMRs of these dose category groups could be estimated as risk.

Table 6 Age–sex distribution of LSS population for each colon dose

Sex	Age at time of bombing	Dose categories (Sv)			
		<0.005 (very low)	0.005 to <0.1 (low)	≥0.1 (high)	Total
Male	0–4	2,040	2,102	911	5,053
	5–9	1,638	1,494	649	3,781
	10–14	2,136	1,895	736	4,767
Female	0–4	2,148	2,122	972	5,242
	5–9	1,576	1,518	654	3,748
	10–14	1,819	1,536	873	4,228

Data refer to Hiroshima and Nagasaki

One possible reason for the low SMRs due to leukemia in this study is that quite a few children died from leukemia in the years before 1950, because the incubation period for pediatric cancer is different from that of adult cancer, especially when age at onset of leukemia and thyroid cancer is young. According to Delongchamp et al. [3], "there is a chance that leukemia deaths went undetected before 1948. There were several deaths before October 1950, and most of these occurred before 1948, when the cause of death is unknown." Their follow-up period was also after 1950, the same as in our study, although their research design is different from ours. Several reviews have supported an association between fetal radiation exposure and childhood leukemia [13, 14]. There is, however, less consensus regarding fetal radiation exposure and solid cancer risk, ranging from suspicions about whether such an effect exists to a study that concluded the total childhood cancer risk is large [4, 13]. In this study we used data since 1950, but it has also been reported by RERF that leukemia in people exposed to the A-bomb occurred relatively soon after the exposure, and looking only at recent years the number of cases does not seem particularly high [24]. Although it is possible that the SMR was underestimated, the width of the 95% CI of SMR for death due to leukemia increased and there was no significant difference, because the number of cases of leukemia was small. Therefore, we cannot conclude that the SMR was low in very low and low dose groups. Longer follow-up will be needed.

SMRs for death due to liver cancer in the VLD group were significantly higher in both males and females (male, SMR = 2.40; female, SMR = 2.81), although SMRs for several causes of death did not show significant differences compared with JPCG in the VLD group of our study. It is possible that factors other than radiation exposure may be a major cause of death from liver cancers, because the SMR for liver cancer has a different trend from cancer of other sites. Because hepatitis virus, which has no association to radiation exposure, is involved in the majority of liver cancers according to several studies, causes other than radiation (e.g., iatrogenic factors) cannot be ruled out. In addition, SMRs for death due to male solid cancer in the LD group might have been significantly high in comparison with JPCG because of high liver cancer mortality. However, it may be difficult to examine our hypothesis because there is little reliable evidence. We also need to consider calendar effects and city differences in liver cancer in further studies with longer follow-up.

Comparisons with a genuine non-exposed control group (JPCG) are important in evaluating primary radiation. A-bomb survivors who were exposed to radiation in childhood are now reaching 65 years old or more, a time at which cancer incidence increases markedly [4]. Therefore, further follow-up of this cohort within a dozen years or so will be important to provide new information on the risks of adult-onset cancers following in childhood primary radiation exposure.

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