Ⅲ Types of late effects – Findings from the field of epidemiology

1 A-bomb survivors

A Malignant tumors

(1) All types of leukemia and solid cancers

Summary

Late effects of A-bomb radiation are diverse, with the most important being carcinogenesis. Risk among the survivors in terms of cancer development varies between solid cancers and leukemia. The period of latency for leukemia is short, having reached a peak only several years after the bombings, and the risk thereafter decreased with each passing year. By 2003, however, the risk of leukemia development had become low, although it had not disappeared entirely. On the other hand, solid cancers have a lengthy latency period and therefore generally only appear for the first time at ages when people typically become prone to developing cancer. After the shortest of all the latency periods, the absolute risk of solid cancers (average excess mortality or incidence rate) increases nearly in proportion with that in the non-exposed population. In other words, relative risk in relation to age or time since exposure remains nearly constant. It also has been suggested that radiation's effects are greater the younger the age at exposure. The radiation dose-response relationship for leukemia can be described by a concave upwardly curved line, whereas the solid cancer dose response is best described by a straight line. As of the end of 2000, nearly all of the A-bomb survivors who were 40 years of age or older at the time of exposure had died, but 90% of those who were young, under the age of 10 at the time of exposure and thus suggested to be highly sensitive to A-bomb radiation's effects, were still alive. Future results from studies of this population will be followed closely.

(a) Introduction

ABCC and RERF have been studying mortality since 1950 in a fixed population (the Life Span Study cohort, LSS) numbering a total of 120,000 persons, consisting of 93,000 survivors of the bombings and 27,000 persons not directly exposed, in order to investigate the health effects of A-bomb radiation. In addition, the two organizations have obtained cancer-incidence data since 1958, from tumor registries in Hiroshima and Nagasaki managed in collaboration with local medical associations, for the conduct of follow-up studies of cancer incidence. The data from the LSS cohort have played a crucial role in the estimation of radiation risk in terms of the population's size, length of follow-up period, and comprehensiveness. This section describes the latest published results from the LSS cohort on mortality and cancer incidence. The main focus is the introduction of results from LSS Report No. 13, which is a comprehensive study of mortality during 1950-97, the study of mortality rate between 1950-2000 that investigated the effects on risks of solid cancers and leukemia due to the changes upon transition from DS86 to DS02, and the results from a study of cancer incidence in the period 1958-98.

To investigate the health effects of radiation in A-bomb survivors, it is essential to have estimates of radiation doses that are as accurate as possible. Over the years, RERF has revised its radiation dosimetry methodology, calculating doses based on T65D (T stands for "tentative"), which was formulated on an interim basis in 1965, then DS86, established in 1986, and DS02, in 2002. Compared with DS86, the γ-ray doses estimated by DS02 increased slightly and neutron doses decreased, but these changes had little effect on the estimation of risk. For assessment of the health effects of A-bomb radiation, doses are configured using weighted dose, defined as the sum of γ-ray dose and 10 times the neutron dose. Among the 93,000 directly exposed A-bomb survivors in the LSS, doses according to DS02 have been estimated for 87,000 people (Table 1). It should be noted that, as of the end of 2000, 90% of people less than the age of 10 at the time of exposure were still alive, whereas almost no survivors were alive who had been aged 40 years or older at the time of exposure (Table 2).

An index is required to indicate the degree of A-bomb radiation effects. The difference in incidence or mortality rates between an exposed group and a control group (defined as those with exposure dose of 0) is called excess absolute risk (EAR), with the ratio of the two called the relative risk (RR). The RR value minus 1 is the excess relative risk (ERR), which represents the ratio of the EAR to the incidence or mortality rate in the comparison control group. Attributable fraction (AF) is used to represent the percentage of cases related to radiation exposure among the total number of observed cases of a certain outcome. AF is the ratio of ERR to RR.

Table 1 Distribution of weighted absorbed colon doses according to DS02 for LSS cohort members

	Hiroshima	Nagasaki	Total
Those with known individual dose (persons)	58,535	28,136	86,671
<5mGy (%)	37.0	59.8	44.6
5～49mGy	29.4	22.1	27.0
50～99mGy	9.5	3.6	7.5
100～499mGy	17.3	7.9	14.2
500～999mGy	4.1	3.7	4.0
1～2Gy	2.0	2.2	2.0
At least 2Gy	0.7	0.7	0.7
Those with unknown individual doses (persons)	3,449	3,621	7,070
Not in city (persons)	20,230	6,350	26,580
Total (persons)	82,214	38,107	120,321

(Preston D.L. et al, Effect of Recent Changes in Atomic Bomb Survivor Dosimetry on Cancer Mortality Risk Estimates, Radiation Research 2004: 162, 575-583)

Table 2 Survival status by age at exposure of LSS cohort members (as of Jan. 1, 2001)

Age at exposure (years)	No. of members (persons)	No. of surviving members
0～9	17,833	15,988 (90%)
10～19	17,563	13,425 (76%)
20～29	10,891	6,490 (60%)
30～39	12,270	2,762 (23%)
At least 40	28,054	261 (0.9%)
Total	86,611	38,926 (45%)

(Preston D.L. et al, Effect of Recent Changes in Atomic Bomb Survivor Dosimetry on Cancer Mortality Risk Estimates, Radiation Research 2004: 162, 575-583)

(b) Cancer development risk

1) All leukemia risk

A risk of all leukemia appeared two to three years following the atomic bombings, peaked seven to eight years later, and thereafter declined continuously, although not disappearing even more than 50 years after exposure. Temporal patterns of leukemia risk differ depending on age at exposure, with the risk increasing the younger the survivors were at the time of bombing but declining rapidly with increasing age. Figure 1 illustrates the temporal patterns of mortality risk of leukemia during 1950-2000 by age at exposure. Such temporal risk patterns show similar results with both DS02 and DS86. Figure 2 indicates DS02 and DS86 doses with regard to the dose-response relationship for leukemia mortality risk during 1950-2000. In either system, the dose-response relationship is not linear; rather, the degree of risk increase is larger the higher the dose, describing a concave upward curve. Leukemia can be classified into, in addition to other types, acute lymphocytic leukemia (ALL), acute myelocytic leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelocytic leukemia (CML). AML is the most prevalent among these types, and thus the all-leukemia numbers are generally thought to reflect the AML results.

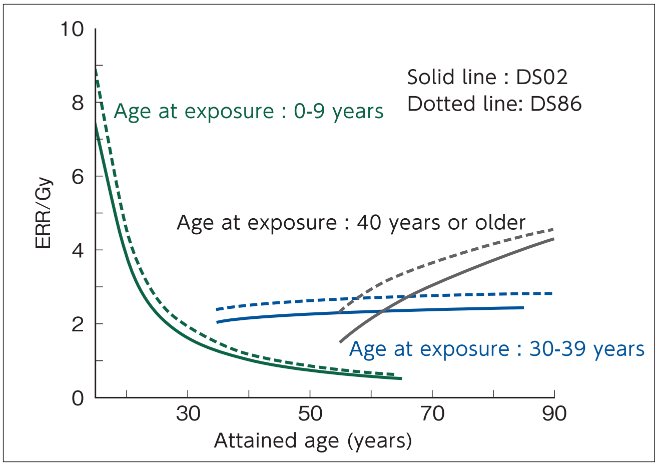

Fig. 1 Temporal changes in mortality risk for leukemia
(Preston D.L. et al, Effect of Recent Changes in Atomic Bomb Survivor Dosimetry on Cancer Mortality Risk Estimates, Radiation Research 2004: 162, 575-583)

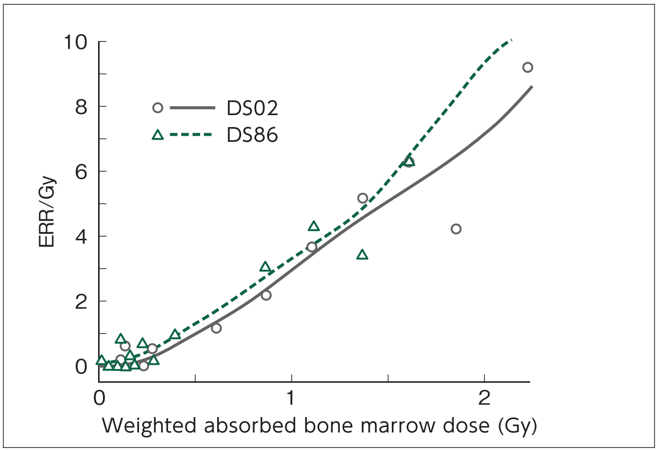

Fig. 2 Dose-response relationship in mortality risk for leukemia
(Preston D.L. et al, Effect of Recent Changes in Atomic Bomb Survivor Dosimetry on Cancer Mortality Risk Estimates, Radiation Research 2004: 162, 575-583)

Table 3 shows numbers of all leukemia deaths and excess deaths by bone marrow dose. A total of 93 cases out of 204 leukemia deaths among those exposed to at least 0.005 Gy are considered to be associated with radiation exposure, an attributable fraction of 46%. At levels of 1 Gy or more, it is estimated that 56 cases among 64 leukemia deaths are associated with radiation exposure, an attributable fraction of 88%

2) Solid cancer risk

For all solid cancers, studies have reported on the mortality risk during 1950-2000, but for less lethal cancers among solid tumors, such as those of the breast, thyroid, and skin, we herein introduce the results of the incidence study conducted during 1958-98. First primary cancers were selected for analysis to avoid the effects of high radiation doses used in cancer treatment, because some of the participants may have had multiple cancers. A total of 17,448 first primary cancer cases were identified during that period.

① Site-specific risk

Figure 3 indicates ERR per 1 Gy and 90% confidence intervals for incidence of all solid cancers and by specific site, after adjustment was made for sex, age, year of birth, and city. As described below, ERR differs by sex, age at exposure, and attained age, and therefore the figure shows sex-averaged ERR for an age of 30 years at the time of bombing and an attained age of 70 years. The ERR for all solid cancers being 0.47, incidence among survivors exposed to 1 Gy rises to 47% in a statistically significant fashion. A statistically significant increase is observed in risks of most cancers, including cancers of the oral cavity, esophagus, stomach, colon, liver, lung, skin (non-melanoma), breast, ovary, bladder, central nervous system, and thyroid. The ERRs for cancers of the pancreas, prostate, and renal cell were not statistically significant, but not inconsistent with the all-solid-cancer ERR. It has been pointed out, however, that cancers of the rectum, gallbladder, and uterus appear to have ERRs lower than that of solid cancers overall. Such results seem to suggest varying radiosensitivities among different sites, and because the confidence intervals overlap at all of the cancer sites with no statistical differences observed among specific sites, caution must be heeded when interpreting the data. Table 4 indicates the sex-averaged ERRs and EARs at an attained age of 70 years for survivors who were aged 10, 30, and 50 years at the time of exposure.

Table 3 Numbers of deaths and estimated excess deaths due to leukemia

Weighted absorbed bone marrow dose (Gy)	Cohort members	Observed person-years	Leukemia deaths	Expected deaths	Estimated excess deaths
< 0.005	37,407	1,376,521	92	84.9	0.1
0.005～0.1	30,387	1,125,891	69	72.1	4.0
0.1～0.2	5,841	208,445	14	14.5	4.7
0.2～0.5	6,304	231,149	27	15.6	10.4
0.5～1	3,963	144,276	30	9.5	18.9
1～2	1,972	71,485	39	4.9	27.7
At least 2	737	26,589	25	1.6	28.2
Total	86,611	3,184,356	296	203.0	93.0

(Preston D.L. et al, Effect of Recent Changes in Atomic Bomb Survivor Dosimetry on Cancer Mortality Risk Estimates, Radiation Research 2004: 162, 575-583)

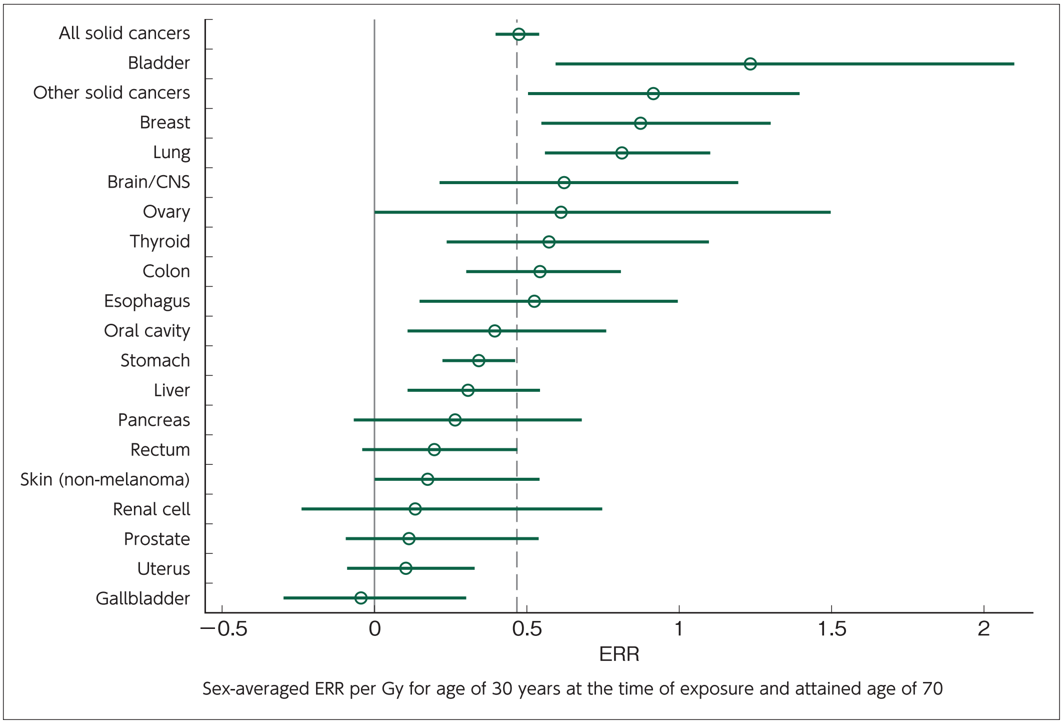

Fig. 3 Excess relative risk (ERR/Gy) by solid cancer site

: 90% confidence interval

(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)

② Risk modifiers

The degree of radiation-induced cancer risk depends on various factors called modifiers. The cancer risk among atomic-bomb survivors varies dramatically by sex, age at exposure, and age (equivalently, time since exposure), and these factors modify radiation risk. Table 5 indicates ERRs by sex and EARs for all solid cancers and for all cancers excluding sex-specific sites (such as breast, uterus, and testes). ERR/Gy for all solid cancers in women was 0.58, 1.6 times higher than the ERR/Gy in men of 0.35. EAR/Gy per 10,000 person-years for the two cancer groupings was 1.4 times higher in women, being 60 versus 43, respectively. Excluding breast, uterus, and testes, the sex ratio for ERR was 1.8 and for EAR 0.9, results that show an ERR nearly twice as high in women as in men but almost no difference in EAR due to sex. The ERR being higher in women than men is because cancer incidence in the non-exposed population is lower in women than men, although the EAR is about the same for both sexes.

Figure 4 indicates changes in sex-averaged solid cancer ERRs and EARs in terms of attained age by age at exposure. Individuals exposed at younger ages had higher ERRs and EARs even at the same attained age, suggesting that younger survivors were more radiosensitive than survivors exposed when older. ERR decreases with attained age, but the degree of decline increases the younger the age at exposure of the survivors. For survivors exposed as adults, the magnitude of decrease is small and the ERR nearly constant. EAR increases with age, reflecting the increase in cancer incidence with age seen in non-exposed populations.

Figure 5 indicates differences in ERR by cancer site due to sex, age at exposure, and attained age. The ERRs clearly do not mirror that of all solid cancers, although the difference is not statistically significant. The sex difference in lung and bladder cancers is larger than that in all solid cancers, but the sex difference in liver cancer is smaller. In the case of colon cancer, ERR in men is higher, in contrast with the higher ERR in women seen in cancers of other sites. In a comparison of ERRs between survivors aged 10 and 40 years at the time of exposure, ERRs in the 10-year-old group are higher for thyroid, gastric, and bladder cancers, the same as seen with all solid cancers. However, in breast and colon cancers, there is almost no difference due to age at exposure, although in the case of lung cancer, ERR is higher for survivors exposed to the bombing at 40 years of age. In a comparison of ERR between attained ages 50 and 75 years, ERR for the 50-year-old group is higher for nearly all cancer sites except bladder cancer, which has a larger ERR for the group with attained age of 75 years.

Table 4 Sex-averaged ERR and EAR by site for ages 10, 30, and 50 years at exposure and attained age of 70 years

Site	Attributable fraction (%)	Excess relative risk (ERR/Gy) by age at exposure (years)			Excess absolute risk (EAR/10,000 person-years-Gy) by age at exposure (years)		
		10	30	50	10	30	50
All solid cancers	10.7	0.67 (0.52, 0.85)	0.47 (0.40, 0.54)	0.32 (0.24, 0.42)	90 (68, 113)	52 (43, 60)	30 (22, 39)
Oral cavity	11.4		0.39 (0.11, 0.76)			0.56 (0.20, 1.2)	
Esophagus	10.2		0.52 (0.15, 1.0)			0.58 (0.18, 1.1)	
Stomach	7.2	0.44 (0.20, 0.83)	0.34 (0.22, 0.47)	0.25 (0.12, 0.44)	9.9 (4.5, 18)	9.5 (6.1, 14)	9.2 (4.2, 16)
Colon	11.4	0.52 (0.21, 1.2)	0.54 (0.30, 0.81)	0.55 (0.15, 1.2)	41 (17, 91)	8.0 (4.4, 12)	1.6 (0.3, 3.9)
Rectum	3.7		0.19 (−0.04, 0.47)			0.56 (−0.13, 1.4)	
Liver	8.1	0.28 (0.06, 0.78)	0.30 (0.11, 0.55)	0.32 (0.07, 0.85)	6.8 (0.0, 22)	4.3 (0.0, 7.2)	2.6 (0.5, 6.4)
Gallbladder	−1.0		−0.05 (<−0.3, 0.3)			−0.01 (<−0.1, 0.51)	
Pancreas	4.8		0.26 (<−0.07, 0.68)			0.46 (−0.13, 1.5)	
Lung	14.7	0.56 (0.26, 1.1)	0.81 (0.56, 1.1)	1.15 (0.69, 1.8)	7.3 (3.4, 14)	7.5 (5.1, 10)	7.8 (4.6, 12)
Skin (non-melanoma)	23.2	2.28 (0.04, 7.8)	0.17 (0.003, 0.55)	0.01 (0.00, 0.08)	2.3 (0.2, 7)	0.35 (0.03, 1.1)	0.05 (0.00, 0.29)
Breast	27.1	0.86 (0.47, 1.5)	0.87 (0.55, 1.3)	0.87 (0.44, 1.5)	23 (15, 34)	9.2 (6.8, 12)	3.7 (2.1, 5.9)
Uterus	1.9		0.10 (−0.09, 0.33)			0.56 (<0, 1.9)	
Ovary	10.3		0.61 (0.00, 1.5)			0.56 (0.02, 1.3)	
Prostate	2.2		0.11 (−0.10, 0.54)			0.34 (−0.64, 1.6)	
Renal cell	2.7		0.13 (−0.25, 0.75)			0.08 (−0.16, 0.44)	
Bladder	16.4	1.32 (0.28, 4.1)	1.23 (0.59, 2.1)	1.15 (0.34, 2.5)	1.8 (0.7, 16)	3.2 (1.1, 5.4)	2.1 (0.5, 4.5)
Brain/CNS	13.0		0.62 (0.21, 1.2)			0.51 (0.17, 0.95)	
Thyroid	24.5	1.21 (0.43, 2.9)	0.57 (0.24, 1.1)	0.27 (0.05, 0.77)	4.0 (1.7, 7.8)	1.2 (0.5, 2.2)	0.4 (0.0, 1.3)
Other solid cancers	16.4	1.65 (0.69, 3.5)	0.91 (0.50, 1.4)	0.51 (0.14, 1.1)	7.7 (3.3, 16)	5.0 (2.7, 7.7)	3.3 (1.1, 6.5)

Figures in parentheses represent 90% confidence intervals; blank spaces for ages at exposure of 10 and 50years indicate that the ERR and EAR for all ages at exposure are the same.
(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)

Table 5 ERR and EAR by sex in all solid cancer incidence

	ERR/Gy			ERR/GyEAR/10,000 person-years-Gy		
	Male	Female	Female/male	Male	Female	Female/male
All solid cancers	0.35	0.58	1.6	43	60	1.4
Non-gender-specific solid cancers	0.34	0.61	1.8	48	44	0.9

(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)

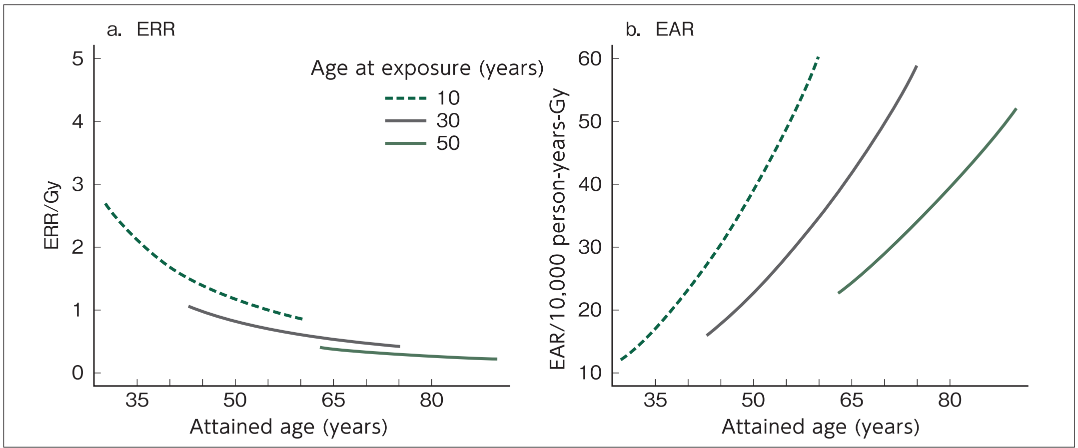

Fig. 4 Age dependence in sex-averaged excess relative risk (ERR/Gy) and excess absolute risk (EAR/10,000person-years-Gy) at 10, 30, 50 years of age at exposure for all solid cancers
(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)

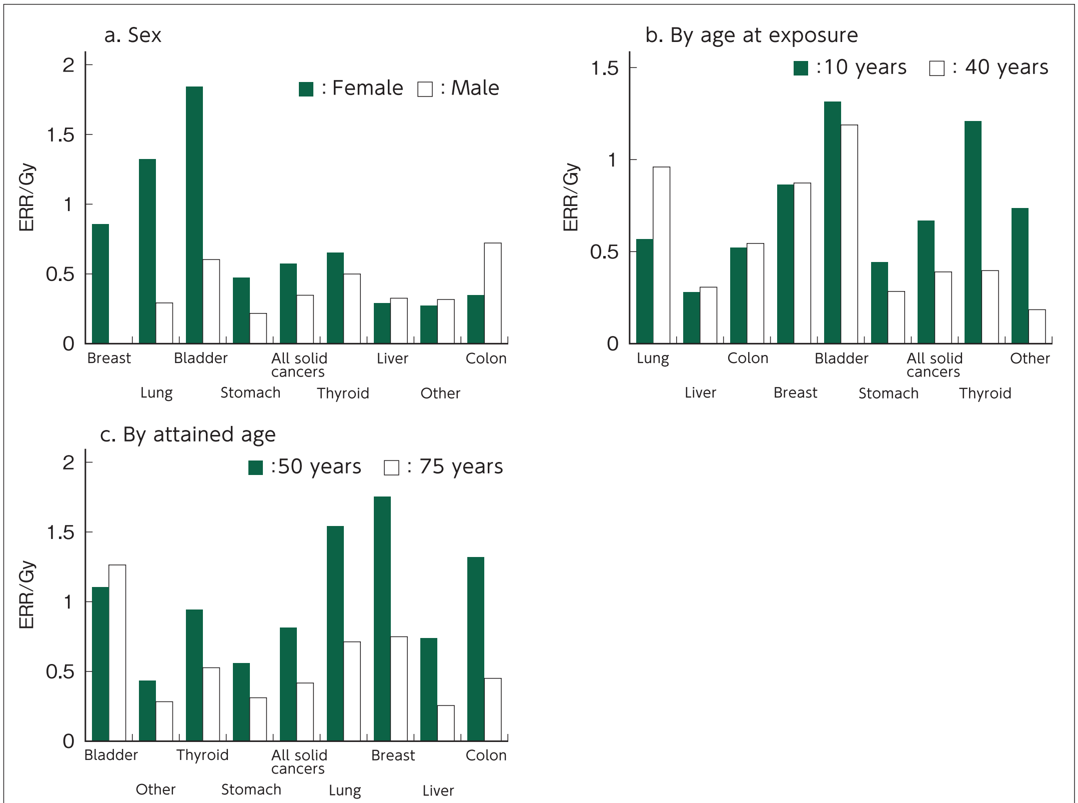

Fig. 5 Excess relative risk (ERR/Gy) for all solid cancers and site-specific cancers by sex (30 years of age at exposure and 70 years attained age), by age at exposure (10 years and 40 years of age at exposure and sex-averaged attained age of 70 years), and by attained age (30 years and 50 years of age at exposure and sex-averaged attained age of 75 years)
(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)

③ Dose-response relationship

Radiation doses in the LSS cohort range widely from low to high. Assessment of low-dose exposure risks is made possible by determining the dose-response curve. The dose response for solid cancers at exposures of less than 2 Gy increases with increasing dose, but at 2 Gy and higher, the dose response is flat (see Fig. 6). While the reason for the flat curve at high doses remains unclear, it is hypothesized to be due to uncertainty in dose estimates or effects of apoptosis (in which cancer does not develop because cells die before they become cancerous). In the range of doses less than 2 Gy, a linear relationship was suggested, with no statistically significant non-linearity. The dose response adheres to a linear relationship at most cancer sites, such as gastric, lung, and breast. Non-melanoma skin cancer seems to follow a threshold model with no risk below 1 Gy.

Because many low-dose survivors are included in the LSS cohort, a dose response has also been observed in terms of incidence of solid cancers in survivors exposed to low doses of less than 0.5 Gy. Consistent with a linear relationship even in the low-dose range, the risk estimates were the same as those estimated for the dose range of 0-2 Gy. A threshold value, should one exist, is not expected to exceed 0.085 Gy.

Estimation of the minimum dose at which increased risk becomes statistically significant is of great interest. The minimum dose for all solid cancers in a report issued by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) was 0.2 Sv based on the mortality data during 1950-2000 and 0.25 Sv in terms of the cancer incidence data during 1958-98. Because they were low, the risk results did not reach statistical significance. However, this does not mean that low-dose risks are zero. Furthermore, because the risk at low doses is low, care must be taken regarding the fact that effects of confounding factors, dose-estimation accuracy, disease classification errors, and so on, are larger on a relative basis with low doses than with high doses.

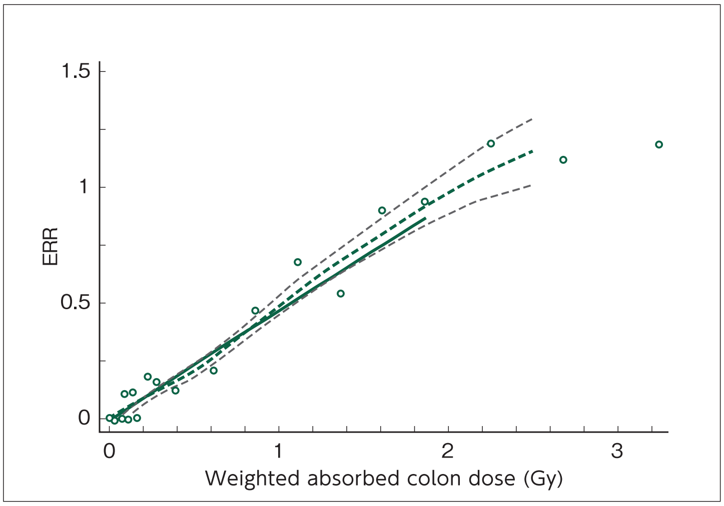

Fig. 6 Dose-response relationship in all solid cancer incidence risk

The solid line represents the estimated straight line for sex-averaged ERR for age at exposure of 30 years and attained age of 70 years within the range of 0-2 Gy; the open dots represent non-parametric estimates;
the bold dotted line represents the smoothed line of non-parametric estimated values; and the fainter two dotted lines represent plus and minus one standard error of the bold dotted line.
(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)

④ Attributable fraction

A-bomb survivors are also exposed to smoking and other carcinogenic factors besides A-bomb radiation, and thus not all cancer incidence among the survivors is attributable to the atomic bombings. For cancer incidence among the atomic-bomb survivors, it is important to express the proportion of A-bomb radiation's contribution. Table 6 shows the numbers of all solid cancers by colon dose and of excess incidence. For doses of at least 0.005 Gy, for example, 850 cases among 7,851 solid cancers were estimated to have been associated with radiation exposure, an attributable fraction of 11%. With exposures of 2 Gy and greater, estimates indicate that 111 among 185 solid cancer cases at all sites are associated with radiation exposure, an attributable fraction of 61%.

Table 6 Incidence and estimated excess incidence of all solid cancers

Weighted absorbed colon dose (Gy)	Cohort members	Observed person-years	Solid cancer incidence	Expected incidence	Estimated excess incidence	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	853	10.7%※

※ : Attributable fraction among people with dose greater than 0.005 Gy.
(Preston D.L. et al, Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998, Radiation Research 2007: 168, 1-64)