RADIATION RESEARCH **177**, 229–243 (2012)
0033-7587/12 $15.00

DOI: 10.1667/RR2629.1

Studies of the Mortality of Atomic Bomb Survivors, Report 14, 1950–2003: An Overview of Cancer and Noncancer Diseases

Kotaro Ozasa,[a,1] Yukiko Shimizu,[a] Akihiko Suyama,[a] Fumiyoshi Kasagi,[a,b] Midori Soda,[a] Eric J. Grant,[a] Ritsu Sakata,[a] Hiromi Sugiyama[a] and Kazunori Kodama[c]

[a] *Department of Epidemiology and* [c]*Chief Scientist, Radiation Effects Research Foundation, 5-2 Hijiyama-koen, Minami-ku, Hiroshima, 732-0815, Japan; and* [b] *Institute of Radiation Epidemiology, Radiation Effects Association 1-9-16, Kaji-cho, Chiyoda-ku, Tokyo, 101-0044, Japan*

Ozasa, K., Shimizu, Y., Suyama, A., Kasagi, F., Soda, M., Grant, E. J., Sakata, R., Sugiyama, H. and Kodama, K. Studies of the Mortality of Atomic Bomb Survivors, Report 14, 1950–2003: An Overview of Cancer and Noncancer Diseases. *Radiat. Res*. 177, 229–243 (2012).

This is the 14th report in a series of periodic general reports on mortality in the Life Span Study (LSS) cohort of atomic bomb survivors followed by the Radiation Effects Research Foundation to investigate the late health effects of the radiation from the atomic bombs. During the period 1950–2003, 58% of the 86,611 LSS cohort members with DS02 dose estimates have died. The 6 years of additional follow-up since the previous report provide substantially more information at longer periods after radiation exposure (17% more cancer deaths), especially among those under age 10 at exposure (58% more deaths). Poisson regression methods were used to investigate the magnitude of the radiation-associated risks, the shape of the dose response, and effect modification by gender, age at exposure, and attained age. The risk of all causes of death was positively associated with radiation dose. Importantly, for solid cancers the additive radiation risk (i.e., excess cancer cases per 10^4 person-years per Gy) continues to increase throughout life with a linear dose–response relationship. The sex-averaged excess relative risk per Gy was 0.42 [95% confidence interval (CI): 0.32, 0.53] for all solid cancer at age 70 years after exposure at age 30 based on a linear model. The risk increased by about 29% per decade decrease in age at exposure (95% CI: 17%, 41%). The estimated lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy, and a formal dose-threshold analysis indicated no threshold; i.e., zero dose was the best estimate of the threshold. The risk of cancer mortality increased significantly for most major sites, including stomach, lung, liver, colon, breast, gallbladder, esophagus, bladder and ovary, whereas rectum, pancreas, uterus, prostate and kidney parenchyma did not have significantly increased risks. An increased risk of non-neoplastic diseases including the circulatory, respiratory and digestive systems was observed, but whether these are causal relationships requires further investigation. There was no evidence of a radiation effect for infectious or external causes of death.

INTRODUCTION

The Radiation Effects Research Foundation (RERF), and its predecessor the Atomic Bomb Casualty Commission (ABCC), has conducted a mortality study since 1950 on a fixed population [Life Span Study (LSS) cohort] of about 120,000 subjects including atomic bomb survivors and residents of Hiroshima and Nagasaki who were not in either city at the time of the bombing to determine the late health effects of ionizing radiation derived from the atomic bombs in Hiroshima and Nagasaki. Periodic analyses of the LSS mortality data have resulted in a series of LSS Reports (*1, 2*). This is the 14th report in the series, which covers the period 1950–2003, including an additional 6 years of follow-up since the last comprehensive report (*2*). The impact of changing to the DS02 dosimetry system (*3*) from the earlier DS86 system on radiation risk estimates has been reported for mortality from all solid cancer and leukemia through 2000 (*4*). The risk of radiation for solid cancer incidence through 1998 was also reported (*5*). However, this is the first time the DS02 dosimetry system has been used while examining mortality from a wide range of causes of death.

The most important finding regarding the late effects of A-bomb radiation exposure on mortality is an increased risk of cancer mortality throughout life (*2*). The rates of excess solid cancer deaths have continued to increase in approximate proportion to radiation dose as the cohort ages. Significant radiation-associated increases in risk have been seen for most sites of solid cancer. The dose–response relationship for these sites has tended to show an approximately linear increase with radiation dose. The relative risks for many cancer sites were higher in those exposed as children. The relative risks declined with increasing attained age of the subjects as well as the number of years after the bombing, although the excess absolute rates continued to increase with attained age. In

[1] Address for correspondence: Department of Epidemiology, Radiation Effects Research Foundation, 5-2 Hijiyama-park, Minami-ku, Hiroshima, 732-0815, Japan; e-mail: ozasa@rerf.or.jp.

TABLE 1
Number of LSS Cohort Members by DS02 Dose, City and Sex

	Subjects with known DS02 dose[a] [weighted colon dose (Gy)]										
	Total	<0.005	0.005–	0.1–	0.2–	0.5–	1.0–	2.0+	Unknown[b]	NIC[c]	Total
Total	86,611	38,509	29,961	5,974	6,356	3,424	1,763	624	7,058	26,529	120,321
Hiroshima	58,494	21,697	22,733	5,037	5,067	2,373	1,152	435	3,442	20,179	82,214
Nagasaki	28,117	16,812	7,228	937	1,289	1,051	611	189	3,616	6,350	38,107
Male	35,687	15,951	12,342	2,382	2,482	1,414	813	303	3,287	11,143	50,175
Female	50,924	22,558	17,619	3,592	3,874	2,010	950	321	3,771	15,386	70,146

Note. Among the total of 120,321subjects, 123 were unavailable for the study because of misidentification or insufficient information.

[a] These numbers exclude the NIC and unknown-dose groups. This group was used for estimating radiation effects.

[b] Those with unknown doses had insufficient location information or were in complex shielding situations where dose could not be estimated reliably.

[c] NIC: Not in the cities of Hiroshima or Nagasaki at the time of bombing.

contrast, the risk of leukemia increased in the early period after the bombing and then decreased, and the dose–response relationship for leukemia showed a linear-quadratic association (*6, 7*). Those different onset and dose–response patterns imply a different pathogenesis between leukemia and solid cancer.

This report provides an overview of the updated results and characterizes the risk of radiation based on the DS02 dosimetry system for total deaths and major causes of death including solid cancer, leukemia and various types of noncancer disease. Due to the elongation of the follow-up period compared to the previous reports and the consequent increased number of outcomes, new findings have emerged for the risks of radiation for cancer and noncancer disease mortality. The purpose of this report is to (1) compare the mortality from a wide range of causes of death using a common model as an overview, (2) conduct more detailed analyses on dose–response relationships and effect modification by age at exposure and attained age, and (3) describe changes in the shape of the dose response for solid cancer and noncancer diseases over the long observation period. A discussion on the effects at low exposure levels such as dose and dose-rate effectiveness factor (DDREF) was also included. For leukemia, since detailed analyses have recently been reported for mortality over the period 1950–2000 based on the DS02 dosimetry system (*7*), further detailed analyses were not conducted.

MATERIALS AND METHODS

Study Population and Follow-Up

The LSS cohort includes a large portion of the atomic bomb survivors who were within 2.5 km of the hypocenters at the time of the bombings, together with an age- and sex-matched sample of people who were between 2.5 and 10 km from the hypocenters. The cohort also includes a sample of about 26,000 persons who were registered as residents of either Hiroshima or Nagasaki in 1950 but were not in the cities (NIC) at the time of the bombings. LSS Report 8 and the later LSS reports have excluded the NIC group from analyses of radiation risk because of concerns about the comparability of their mortality rates to those for other zero-dose cohort members, likely due to sociodemographic or other differences (*1, 8, 9*). The subjects were recruited from the 1950 Japanese National Census, which had a supplementary questionnaire about A-bomb exposures, plus two surveys conducted by the Atomic Bomb Casualty Commission (ABCC) in 1950 and 1951, and the resident surveys by Hiroshima and Nagasaki cities in 1953 and 1950, respectively (*1*). Comprehensive mortality follow-up began on October 1, 1950 (*1*). The final number of subjects was 120,321 members (82,214 in Hiroshima and 38,107 in Nagasaki) (*10*). Among them, 123 subjects were unavailable for the study and were excluded from the analyses because of misidentification or insufficient information. Individual DS02 dose estimates are available for 86,611 survivors. Another 7,058 survivors do not have dose estimates, mainly due to insufficient or uncertain information on location and shielding at the time of the bombing, and were excluded from these analyses (*11*). The total number of subjects and the distribution of DS02 dose categories by city and sex are shown in Table 1.

Mortality follow-up was facilitated by the family registry system (*koseki*), which covers the whole of Japan and is >99% complete. A small number were lost to follow-up due to migration out of the country and were censored at the time of emigration. In this report, follow-up data until December 31, 2003 were analyzed. We found 19 individuals who were born before 1900 and presumed to be alive by the *koseki* as of January 1, 2004 (104 years of age or older). They were checked at municipal office registries: five were documented as alive, six migrated to other countries, seven were deleted from the residence registries because the municipality offices could not confirm their residence status, and no information was obtained for one person. The six individuals who migrated overseas were treated as censored at the time of migration. The seven individuals who were deleted from residence registries were treated as deceased at the time of deletion due to unknown causes. The one with no information was treated as censored at the end of the follow-up.

Cause of death for the subjects was classified by trained staff in the ABCC/RERF according to the International Classification of Diseases (ICD), 7th to 10th editions (*12–15*). The list of disease categories, corresponding ICD numbers, and applicable years are shown in the Appendix found on page 243. We analyzed all solid cancer, cancer of major sites, hemato-lymphoid malignancies, and broad classifications of noncancer diseases including diseases of the blood and blood-forming organs, circulatory system, respiratory system, digestive system, and genitourinary system, infectious and parasitic diseases, and external causes.

Dosimetry

This report is the first to apply DS02, which includes a number of improvements over the previous system (*3, 11*), to the mortality experience from a wide range of causes of death in the LSS Report series. The primary systematic change effected by DS02 was an increase of about 10% in γ-ray estimates for both Hiroshima and

Nagasaki, consequently causing the estimated risks from radiation exposure to be slightly lower than before (*4*). Weighted dose, which is the sum of the γ-ray dose plus 10 times the neutron dose, was used to allow for the greater biological effectiveness of neutron doses and is expressed in units of gray (Gy). Although the relative biological effectiveness (RBE) of neutrons is thought to be a decreasing function of dose, with values possibly higher than 10 at low doses, we could not precisely estimate the neutron RBE for the atomic bombs of Hiroshima and Nagasaki. Therefore, we used a constant RBE of 10, which has been used previously (*6, 27*).

DS02 includes calculated doses for 15 organ sites. In keeping with past reports, analyses of all solid cancer used colon dose as representative for all organs, while those of hemato-lymphoid malignancies used the dose to bone marrow. Analyses for site-specific cancers and noncancer diseases of major organs used corresponding specific organ doses. For individual dose estimates, shielded kerma estimates above 4 Gy (317 members) were truncated to 4 Gy because they are likely to represent misinformation on exposure factors such as shielding or exact location. To correct for dose uncertainties due to random measurement error, unadjusted DS02 estimates were replaced by expected survivor dose estimates using the method developed by Pierce *et al*. (*16*) and assuming 35% measurement error in individual doses.

Statistical Methods and Organization of Data for Analysis

Poisson regression methods for grouped survival data were used to describe the dependence of risk on radiation dose and to evaluate the variation of the dose response with respect to city, sex, age at exposure, and attained age (*17*). Significance tests and confidence intervals (CI) were based on likelihood ratio statistics. The results were considered statistically significant when the two-sided $P < 0.05$.

The models used here, which were also used in previous reports (*2, 5*), are as follows.

Excess Relative Risk (ERR) model:

$$\lambda_0(c,s,b,a)[1+\mathrm{ERR}(d,s,e,a)],$$

Excess Absolute Risk (EAR) model:

$$\lambda_0(c,s,b,a)+\mathrm{EAR}(d,s,e,a),$$

where λ_0 is the baseline or background mortality rate at zero dose, depending on city (c), sex (s), birth year (b), and attained age (a). λ_0 was modeled by stratification for the ERR model and by parametric function involving relevant factors for the EAR model. ERR or EAR depends on radiation dose (d) and, if necessary, effect modification by sex, age at exposure (e), and attained age. In effect, the ERR and EAR functions are described as parametric functions of the form $\rho(d)\varepsilon(e,s,a)$, in which $\rho(d)$ describes the shape of the dose–response function and $\varepsilon(s,e,a)$ describes the effect modification.

First, we estimated ERR for major causes of death using a linear dose–response model (L) ($\rho(d) = \beta_1 d$) without effect modification because this simple model can be applied to most cancer sites to compare them in a common way. The ERR model is as follows:

$$\lambda_0(c,s,b,a)[1+\beta_1 d].$$

For leukemia, a linear-quadratic model (LQ) ($\rho(d) = \beta_1 d + \beta_2 d^2$) was used since previous LSS reports have indicated that it had the best dose response for leukemia among the LSS (*4, 7*).

Next, we took account of effect modification by sex, age at exposure, and attained age in the linear dose model for ERR and EAR, respectively, for all solid cancer and cancer of selected sites because the model can estimate the radiation risks more accurately and also can be applied to selected major sites with sufficient numbers of excess cases. Effect modification was described using multiplicative-function models as follows:

$$\varepsilon(e,s,a) = \exp(\tau e + \upsilon \ln(a))(1+\sigma s),$$

where τ, υ and σ were the coefficients for effect modification by age at exposure, attained age, and sex, respectively. The term that includes sex ($s = 1$ for men and $s = -1$ for women) as a modifier allows the β_1 parameter to represent sex-averaged risk estimates. Therefore, ERR and EAR models were, respectively,

$$\lambda_0(c,s,b,a)[1+\beta_1 d\cdot\exp(\tau e+\upsilon\ln(a))\cdot(1+\sigma s)];$$

$$\lambda_0(c,s,b,a)[\beta_1 d\cdot\exp(\tau e+\upsilon\ln(a))\cdot(1+\sigma s)].$$

In addition to the simple L model, we have considered LQ and pure quadratic (Q) ($\rho(d) = \beta_2 d^2$) models with effect modification (by sex, age at exposure, and attained age) for all solid cancers. The curvature of the dose response was examined using the ratio of the quadratic and linear coefficients ($\theta = \beta_2/\beta_1$) in the LQ model. θ can range from zero for a pure linear model to infinity for a pure quadratic model.

To evaluate the radiation effects in limited dose ranges, the ERRs for all solid cancer for selected dose ranges were estimated based on the linear model with effect modification by sex, age and age at exposure [$\mathrm{ERR} = (\beta_l d + \beta_h d)\exp(\tau e + \upsilon \ln(a)\cdot(1+\sigma s))$], where $\beta_l d$ is the coefficient for the lower dose range and $\beta_h d$ for the higher dose range. Coefficients for the effect modification terms were common to the two parts of the dose range. The lowest dose range with a statistically significant ERR dose response for all solid cancer was estimated by testing the null hypothesis that the low-dose slope was zero by stepping up the cut point by 0.01 Gy. Threshold doses for all solid cancer were also estimated using the linear model as $\rho(d) = \beta_l(d - d_0)$ for $d > d_0$ or $\rho(d) = 0$ for $d \le d_0$, where d_0 was the threshold, and adjusted for sex, age and age at exposure with modification by sex, age and age at exposure. A wide range of possible values for d_0 were examined by stepping up by 0.01 Gy, and the point with the greatest maximum likelihood value was determined. The minimum deviance was used to determine the dose threshold and the dose yielding a deviance of the minimum plus 3.84 (which corresponds to χ^2 1 degree of freedom cutoff point) determined its upper and lower 95% CI. If the lower limit of the 95% CI of the threshold exceeded 0 Gy, we would conclude that a threshold exists, while the upper limit indicates the maximum threshold value that is compatible with the data.

It has been suggested that the LSS cohort constructed in 1950 suffers from selection bias in that members of the cohort who survived from the time of bombings to 1950 may have been healthier and hence more resistant to the radiation effects (*2, 18*). To investigate this effect, the dose–response relationships of noncancer diseases were evaluated using an LQ model without effect modification for both the early period of follow-up (1950–1965) and the later period (1966–2003) using an ERR model. For reference, the same analysis was also conducted for all solid cancer using the linear-quadratic model with effect modification by sex, age at exposure, and attained age. Attributable fractions were estimated from the numbers of radiation-associated excess deaths and the corresponding total numbers of deaths from solid cancer and noncancer diseases except for non-neoplastic blood diseases based on the linear ERR model with effect modification by sex, age at exposure, and attained age to allow comparisons between the two classes of outcomes. CIs for estimating excess deaths were estimated by the multivariate delta method.

Analyses are based on detailed tabulations of the data cross-classified by city, sex, age at exposure, attained age, follow-up period, and radiation dose. The categories of age at exposure were 5-year categories for ages 0 through 69 and 70 or more. Attained age was categorized by 5-year intervals for ages 5 though 99 plus 100 or more. The dose category cut points were 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.15, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5 and 3 Gy. The follow-up period was divided into 5-year intervals.

TABLE 2
Observed Person-Years and Number of Deaths in the LSS Cohort Members with Known DS02 Doses, as of January 1, 2004, by Age at Exposure

Age at exposure (years)	Number of subjects	Observed person-years	Number of deaths[a]	Alive
0–9	17,833	910,347	2,200	88%
10–19	17,563	848,826	4,887	72%
20–29	10,891	494,021	5,178	52%
30–39	12,270	462,694	10,410	15%
40–49	13,504	365,240	13,397	1%
50+	14,550	213,079	14,548	0%
Total	86,611	3,294,210	50,620	42%

[a] These numbers do not include the subjects who were NIC, unknown dose, or censored because of deletion from *koseki* by municipality offices and other reasons.

The basic data for each cell in the tabulations were the number of deaths for specific causes and time at risk in terms of person-years. The cell-specific mean values were included for γ-ray and neutron dose and each age/time variable. Parameter estimation and tests were based on likelihood using Epicure software (*19*). When the lower limit was not estimable, an implicit lower bound on the ERR was thought to be $-1/d\_\max$, where $d\_\max$ was the maximum individual dose.

RESULTS

Among the 86,611 subjects with estimated DS02 doses, 50,620 subjects (58%) died in the follow-up period (Table 2). While 99.6% of those who were exposed to A-bomb radiation at age of 40 years or older had died, fully 80% of those under age 20 at that time were still alive. The numbers of subjects who died of specific causes of death is shown in Table 3. Twenty-two percent of deaths were due to solid cancer, 1.4% to lymphoid and hematopoietic malignancies, 71% to non-neoplastic diseases, and 5% to external causes.

Site-Specific Cancer Excess Risks

Radiation risks for major causes of death, including major cancer sites, are shown in Fig. 1 (ERRs in the simple L model). The ERR per Gy (ERR/Gy) for total deaths was statistically significant, 0.22 (95% CI: 0.18, 0.26). Also the risk estimate for all solid cancer was 0.47 (95% CI: 0.38, 0.56). The highest ERR was observed for cancer of the renal pelvis and ureter, then cancers of the breast (female only), other digestive system, bladder, ovary (female only), lung, colon, esophagus, gall bladder, liver and stomach in descending order, although the CIs for these estimates overlapped considerably. The ERR estimate for renal pelvis and ureter was notably unstable because of the small number of cases. Other cancers such as rectum, pancreas, uterus (female only), prostate (male only), or kidney parenchyma did not have significantly increased risks.

Sex-specific ERRs along with 95% CIs are shown in Table 3. The sex-specific ERR/Gy in females was around twice as high as that in males for both total deaths and all solid cancer. The ERRs for cancers of most sites were also higher in females. There were some notable differences in the magnitude of radiation effects between sexes. Cancer of the gallbladder and renal pelvis and ureter had increased risks in males but not in females, whereas cancers of the stomach, rectum and other digestive diseases showed increased radiation risk in females but not in males; however, the CIs for males and females overlapped in all cases.

The sex-averaged ERR of leukemia was 3.1 (95% CI: 1.8, 4.3) at 1 Gy and 0.15 (−0.01, 0.31) at 0.1 Gy in the LQ model. However, the ERR was not significant for malignant lymphoma or multiple myeloma (Fig. 1). There were some apparent sex differences; namely, there were significant increases for malignant lymphoma in males only and for multiple myeloma in females only (Table 3).

The estimates of effect modification of the ERR by sex, age at exposure, and attained age are shown in Table 4 for all solid cancer and cancer of the selected major sites. The left column shows the sex-averaged ERR/Gy for the subjects at an attained age of 70 years after exposure at the age of 30. The right columns show the parameter estimates of the effect modifiers. The ERR/Gy for females was around two times higher than males and the ratios were significantly greater than unity for all solid cancer and cancers of the stomach and lung. The ERR/Gy for solid cancer declined −29% per 10-year increase of age at exposure and also declined in proportion to the −0.86 power of attained age, and both effect modifiers were significant, as illustrated in Fig. 2. The age effects for cancers of specific sites were similar to those for all solid cancer, but most were not statistically significant.

The estimates for the same cancers using the EAR model are shown in Table 5 (three sites were omitted because of nonsignificant results in the ERR or effect modification terms in Table 4). The left column shows the sex-averaged EAR/10^4 person-years/Gy. The right columns show the parameter estimates of effect modifiers. There were no sex differences in EAR for all solid cancer or for major individual types of cancer. The EAR significantly declined −19% per 10-year increase in age at exposure for all solid cancer, as illustrated in Fig. 3. Estimates for specific cancer

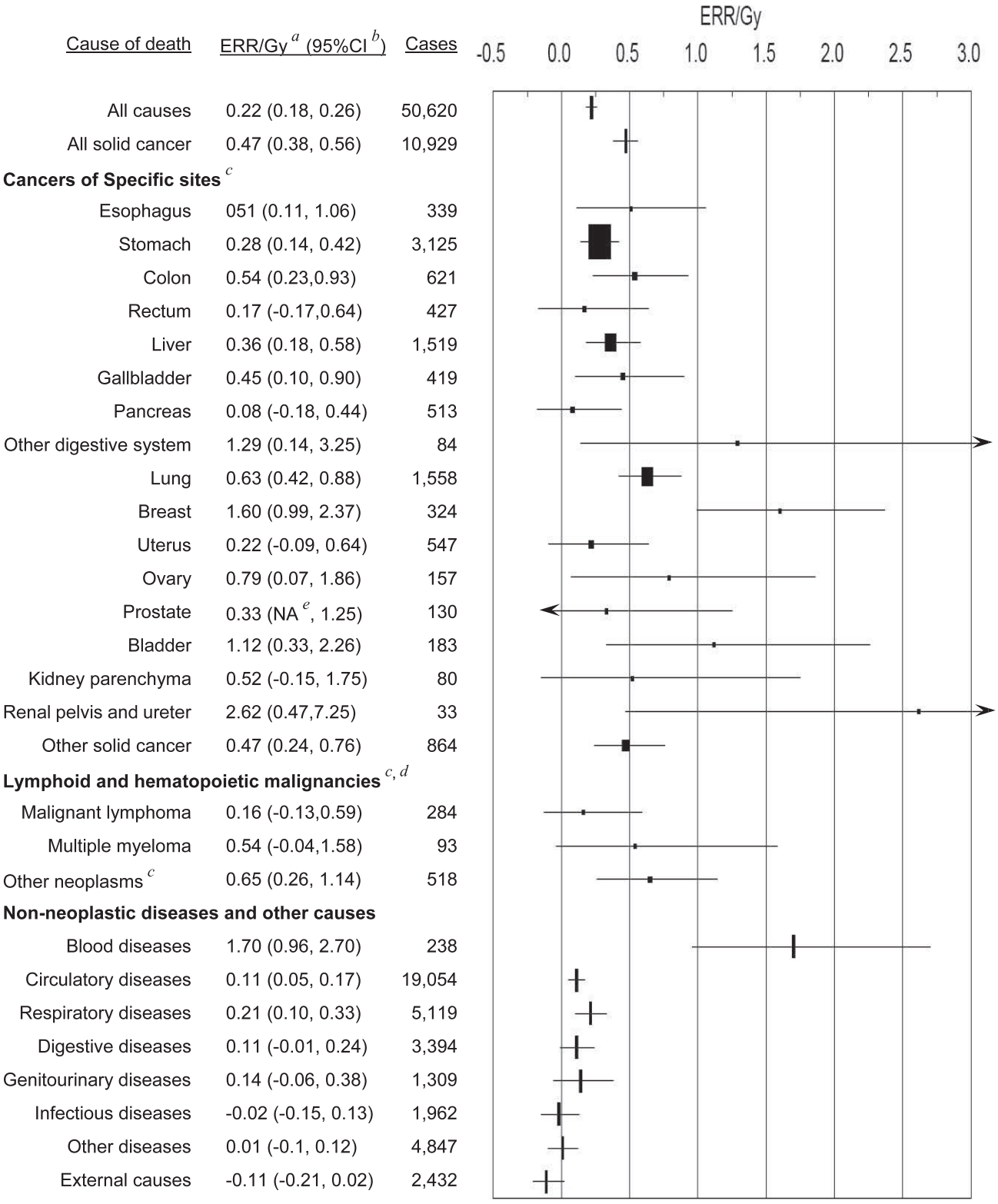

FIG. 1. Estimates of excess relative risk (ERR) per Gy and 95% CI for major causes of death. [a] ERR was estimated using the linear dose model, in which city, sex, age at exposure, and attained age were included in the background rates, but not allowing radiation effect modification by those factors. [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.

TABLE 3
Number of Deaths, Excess Relative Risk (ERR) Estimates per Gy for Specific Causes of Death by Sex

Cause of death	Based on radiation dose to:	Males				Females			
		Number of deaths	ERR/Gy[a]	(95% CI[b])	*P*	Number of deaths	ERR/Gy[a]	(95% CI[b])	*P*
All causes	Colon	22302	0.15	(0.10, 0.20)	<0.001	28318	0.30	(0.24, 0.35)	<0.001
Cancer									
All solid cancer	Colon	5235	0.31	(0.21, 0.42)	<0.001	5694	0.66	(0.52, 0.80)	<0.001
Esophagus	Stomach	260	0.39	(−0.006, 0.97)	0.054	79	1.1	(0.04, 3.0)	0.04
Stomach	Stomach	1689	0.13	(−0.02, 0.30)	0.09	1436	0.51	(0.28, 0.78)	<0.001
Colon	Colon	262	0.50	(0.09, 1.09)	0.01	359	0.58	(0.16, 1.1)	0.003
Rectum	Bladder	199	–0.26	(NA[c], 0.19)	0.18	228	0.66	(0.06, 1.5)	0.03
Liver	Liver	879	0.30	(0.08, 0.58)	0.006	640	0.46	(0.15, 0.85)	0.002
Gallbladder	Liver	121	0.85	(0.19, 1.9)	0.005	298	0.23	(−0.12, 0.76)	0.24
Pancreas	Pancreas	210	0.22	(−0.17, 0.83)	0.33	303	–0.06	(NA[c], 0.43)	>0.5
Other digestive system	Colon	33	0.26	(NA[c], 2.33)	>0.5	51	2.6	(0.51, 6.6)	0.005
Lung	Lung	901	0.40	(0.17, 0.67)	<0.001	657	1.1	(0.68, 1.6)	<0.001
Breast	Breast	6	9.1	(0.52, 128)	0.01	324	1.5	(0.93, 2.3)	<0.001
Uterus	Uterus	–				547	0.22	(−0.09, 0.64)	0.19
Ovary	Ovary	–				157	0.79	(0.07, 1.9)	0.03
Prostate	Bladder	130	0.33	(NA[c], 1.2)	0.30	–			
Bladder	Bladder	100	0.88	(0.02, 2.3)	0.04	83	1.5	(0.21, 3.8)	0.02
Kidney parenchyma	Colon	42	0.11	(NA[c], 1.4)	>0.5	38	1.5	(0.01, 4.9)	0.049
Renal pelvis and ureter	Colon	13	3.5	(0.25, 14)	0.02	20	1.9	(NA[c], 8.0)	0.13
Other	Colon	390	0.36	(0.02, 0.83)	0.04	474	0.54	(0.14, 1.0)	0.005
Lymphoid and hematopoietic malignancies									
Leukemia	Bone marrow	163	4.6	(3.0, 6.9)	<0.001	155	3.9	(2.5, 6.1)	<0.001
Malignant lymphoma	Bone marrow	125	0.70	(0.08, 1.7)	0.02	159	–0.18	(−0.21, 0.24)	0.33
Multiple myeloma	Bone marrow	34	0.11	(NA[c], 1.6)	>0.5	59	0.86	(0.02, 2.5)	0.04
Other neoplasms	Colon	224	0.30	(−0.10, 0.88)	0.17	294	1.1	(0.44, 2.0)	<0.001
Non-neoplastic diseases									
Blood diseases	Bone marrow	80	1.8	(0.68, 3.8)	<0.001	158	1.6	(0.76, 2.8)	<0.001
Circulatory disease	Colon	7607	0.07	(−0.001, 0.16)	0.053	11447	0.14	(0.06, 0.23)	<0.001
Respiratory disease	Colon	2401	0.16	(0.02, 0.31)	0.02	2718	0.28	(0.11, 0.47)	<0.001
Digestive disease	Colon	1659	0.05	(−0.09, 0.23)	0.50	1735	0.18	(−0.01, 0.40)	0.07
Genitourinary disease	Colon	449	–0.07	(NA[c], 0.28)	>0.5	860	0.28	(0.01, 0.62)	0.04
Infectious disease	Colon	1043	0.01	(−0.16, 0.22)	>0.5	919	–0.07	(NA[c], 0.18)	>0.5
Other disease	Colon	1830	0.03	(−0.12, 0.21)	>0.5	3017	–0.01	(−0.15, 0.15)	>0.5
External causes	Colon	1372	–0.24	(NA[c], −0.11)	0.001	1060	0.14	(−0.07, 0.41)	0.21

[a] ERR was estimated using the linear dose model, in which city, age at bombing, and attained age were included in the background rates, but not as radiation effect modifiers.

[b] The lower limit was not estimable, but an implicit lower bound (1/d_max) was −0.28 for males and −0.27 for females (see text).

sites tended to be similar, but most were not significant. The EAR significantly increased as the 3.4 power of attained age as an effect modifier for all solid cancer and also significantly increased for cancer of major sites (Table 5).

The fits of the L, LQ and Q models were compared for all solid cancer in the full dose range (left columns of Table 6). They did not show a significant difference of deviances between the L and LQ models ($P = 0.36$), indicating that a quadratic term was unnecessary. The Q model had a significantly worse model fit than the L or LQ models. Furthermore, the L model showed the smallest Akaike Information Criterion (AIC) (*20*), the LQ model had a 1.2-point larger value than the L model, and the Q model was 23.7 points larger, again indicating that it provided the poorest fit. Those differences were calculated from the deviances in Table 6. Consequently, the L model was selected as the best model in the full dose range. Figure 4 shows the estimated plots of dose dependence according to the L and LQ functions.

Although the linear model provided the best fit in the full dose range, statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy ($\theta = 0.81$, $P = 0.02$) (Tables 6 and 7). The curvature over the 0–2-Gy range has become stronger over time, going from $\theta = 0.20$ for the period 1950–1985 to 0.81 for 1950–2003, and has become significant with longer observation (Table 7).

TABLE 4
Effect Modification of the Excess Relative Risk (ERR) Model[a] for Major Cancers

	Sex-averaged ERR/Gy[b]		Sex (σ) (ERR ratio: female/male)		Age at exposure (τ) (Percentage change per 10-year increment)		Attained age (υ) (power)	
		(95% CI[c])		(95% CI)		(95% CI)		(95% CI)
All solid cancer	0.42	(0.32, 0.53)	2.1	(1.4, 3.1)	−29%	(−41%, −17%)	−0.86	(−1.60, −0.06)
Esophagus cancer	0.60	(NA, 1.64)	4.3	(0.54, >100)	35%	(−28%, 184%)	–3.7	(−9.6, 1.0)
Stomach cancer	0.33	(0.17, 0.52)	3.7	(1.3, >100)	−18%	(−47%, 20%)	−0.74	(−2.5, 1.2)
Colon cancer	0.34	(0.05, 0.74)	1.4	(0.39, 6.6)	−3%	(−51%, 63%)	−5.8	(−10.4, −2.2)
Liver cancer	0.38	(0.11, 0.62)	1.6	(0.43, 7.9)	−8%	(−62%, 42%)	0.02	(−2.8, 4.2)
Gallbladder cancer	0.48	(0.12, 1.02)	0.42	(<0.001, 2.4)	−27%	(−76%, 40%)	−1.9	(−6.6, 7.8)
Lung cancer	0.75	(0.51, 1.03)	2.7	(1.3, 6.8)	–7%	(−35%, 29%)	–0.04	(−2.2, 2.6)
Breast cancer[d]	0.90	(0.30, 1.78)	–	–	−45%	(−67%, −17%)	−0.17	(−2.7, 2.3)
Bladder cancer	1.19	(0.27, 2.65)	1.7	(0.2, 9.0)	−2%	(−62%, 92%)	0.49	(−3.6, 6.1)
Ovary cancer	0.20	(NA, 1.30)	–	–	−22%	(−96%, 218%)	−4.1	(−33, 1.9)

[a] The ERR model was defined as $\lambda_0(c,s,b,a)\ [1 + \beta_1 d \cdot \exp(\tau\ e + \upsilon \ln(a)) \cdot (1 + \sigma\ s)]$, where d is dose, s is sex, b is birth year, e is age at exposure, and a is attained age. τ, υ and σ are coefficients for effect modification.
[b] The sex-averaged ERR/Gy is shown for subjects at the attained age of 70 years after exposure at age 30.
[c] 95% confidence interval.
[d] Female only.

However, the estimated ERRs under 0.3 Gy were nominally higher than the best-fitting linear slope or the LQ function for either 0–2 Gy or the full dose range in Fig. 4. A quadratic-spline function with a knot at 0.2 Gy that allowed higher estimates at the low-dose level did not provide a significantly better fit than the LQ function ($P = 0.16$). It was particularly notable that the ERR/Gy estimates for linear functions calculated for various low-dose ranges showed higher values for ranges less than 0.1 Gy compared to estimates obtained from higher dose ranges (Fig. 5), i.e., the slope was not shallower in the low-dose range than at high dose levels.

The lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy with an estimated ERR/Gy of 0.56 (95% CI: 0.15, 1.04, $P = 0.01$) and included 74,444 persons with 9,063 solid cancer deaths. For the range of 0 to 0.18, the ERR/Gy was 0.43 (95% CI: −0.0047, 0.91, $P = 0.052$) and included 8,920 deaths (Fig. 5). The maximum likelihood estimate of a dose threshold was 0.0 Gy (i.e., no threshold) with an estimated upper bound of 0.15 Gy for 95% CI as determined by minimizing the deviance.

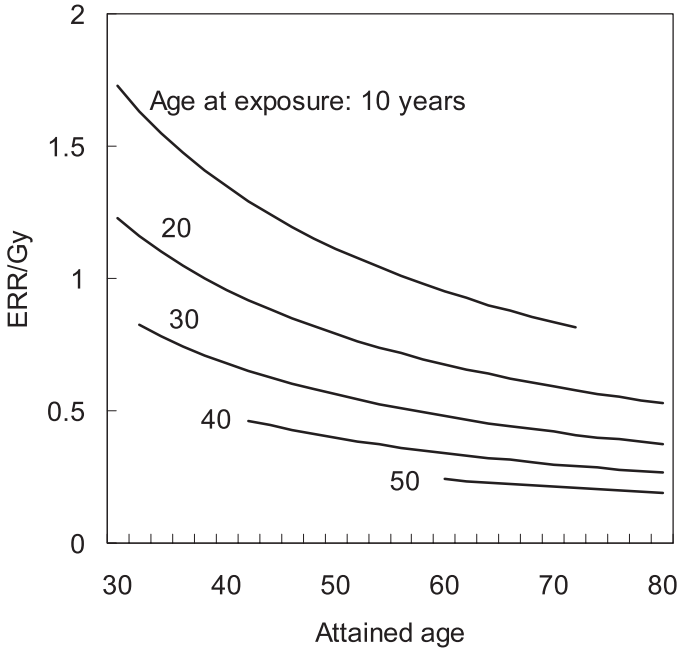

FIG. 2. Modification of the excess relative risk (ERR) for all solid cancer by age at exposure and attained age.

Noncancer Disease Excess Risks

The risks were significantly elevated for non-neoplastic diseases of the blood (ERR/Gy = 1.7, 95% CI: 0.96, 2.7), circulatory system (0.11, 95% CI: 0.05, 0.17), and respiratory system (0.21, 95% CI: 0.10, 0.33). Among the nonmalignant respiratory diseases, the risk of pneumonia and influenza was significantly elevated (ERR/Gy = 0.24, 95% CI: 0.10, 0.40, with 3,244 deaths). Other non-neoplastic diseases including infectious diseases did not show any increased radiation risk in either sex except for genitourinary diseases in females. There were no dose-related excess mortality risks from external causes (Fig. 1, Table 3).

As for the changes in dose response over the long follow-up period, the risks of circulatory, respiratory and digestive diseases were all significantly elevated during the period after 1965 (Table 8). The risk of pneumonia and influenza was also higher in the latter period (ERR/Gy = 0.25, 95% CI: 0.10, 0.43), but liver cirrhosis, a major digestive disease, did not show any increased radiation risk during the whole period or for the period after 1965 (ERR/Gy = 0.11, 95% CI: −0.07, 0.34 and 0.17, 95% CI: −0.04, 0.42, respectively).

TABLE 5
Effect Modification of the Excess Absolute Risk (EAR) Model[a] for Major Cancers

	Sex-averaged EAR/ 10^4 PY/Gy[b]		Sex (σ) (EAR ratio: female/male)		Age at exposure (τ) (Percentage change per 10-year increment)		Attained age (υ) (power)	
		(95% CI)[c]		(95% CI)		(95% CI)		(95% CI)
All solid cancer	26.4	(20.3, 32.8)	1.1	(0.80, 1.74)	–19%	(−31%, −7%)	3.4	(2.7, 4.1)
Stomach cancer	4.1	(2.1, 6.7)	1.8	(0.66, 32)	18%	(−18%, 62%)	2.0	(1.0, 3.6)
Colon cancer	1.6	(0.5, 3.0)	0.98	(0.34, 4.5)	–30%	(−58%, 2%)	3.2	(1.3, 5.3)
Liver cancer	3.4	(0.7, 5.9)	0.69	(0.19, NA)	–25%	(−66%, 15%)	6.0	(3.2, 12)
Lung cancer	6.5	(4.3, 9.0)	0.78	(0.40, 1.8)	–16%	(−37%, 6%)	6.2	(4.5, 8.2)
Breast cancer[d]	2.3	(1.0, 3.8)	–	–	–51%	(−68%, −30%)	3.0	(1.7, 4.7)
Bladder cancer	1.2	(0.3, 2.4)	0.40	(0.0, 5.3)	–1%	(−65%, −80%)	7.5	(3.1, 15)

[a] The EAR model was defined as $\lambda_0(c,s,b,a) + \beta_1 d \cdot \exp(\tau\, e + \upsilon \ln(a)) \cdot (1 + \sigma\, s)$, and parameters are indicated in Table 4.
[b] The sex-averaged EAR/10^4 person-years/Gy is shown for subjects at the attained age of 70 years after exposure at age 30.
[c] 95% confidence interval.
[d] Female only.

The dose–response relationships of noncancer disease mortality for the early period (1950–1965) and late period (1966–2003) of follow-up are shown in Fig. 6. The relationship for the early period (dotted line) showed essentially no radiation effect below about 1.5 Gy while that for the late period showed an approximately linear dose–response relationship for noncancer diseases as a whole, and the difference in shapes was significant between the periods (panel A, $P = 0.02$). Among noncancer diseases, circulatory diseases did not show a difference between the periods (panel B, $P < 0.05$), but both respiratory and digestive diseases showed marginal differences between periods (panel C, $P = 0.07$ and panel D, $P = 0.06$, respectively), and the temporal difference for all solid cancers was not significant (Panel E, $P = 0.18$). A comparison between L and LQ fit for each period showed that the LQ function fit significantly better in the early period for total noncancer diseases ($P = 0.04$) but not for the late period ($P = 0.29$). A similar pattern was found for respiratory diseases ($P = 0.01$ and $P = 0.35$, respectively). There were no differences between the L and LQ fits in either period for circulatory diseases ($P = 0.23$ for the early and $P > 0.5$ for the later), digestive diseases ($P < 0.5$ and $P = 0.22$, respectively), or solid cancer ($P < 0.5$ and $P = 0.39$, respectively).

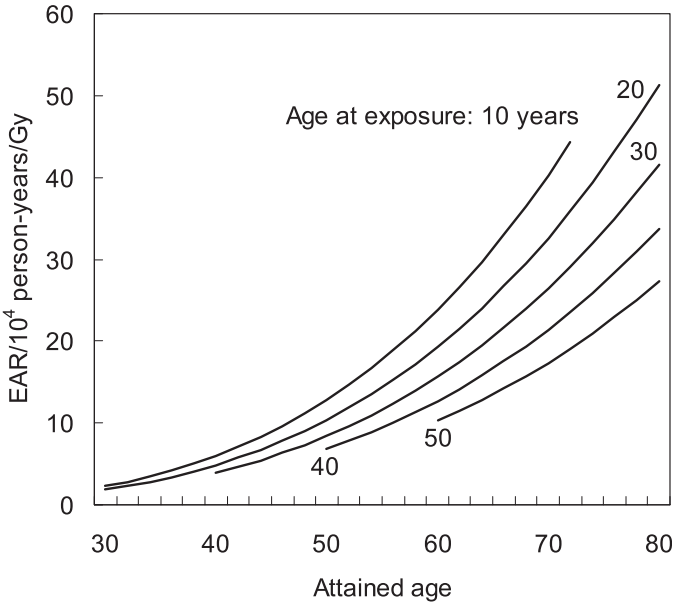

FIG. 3. Modification of the excess absolute risk (EAR) for all solid cancer by age at exposure and attained age.

Estimates of the numbers of radiation-associated excess deaths in the LSS between 1950 and 2003 are shown in Table 9. The excess deaths of solid cancer were estimated as 527 (95% CI: 157, 899). About 8.3% (=525/6308) (95% CI: 2.6%, 14%) of the deaths among cohort members with colon dose of 0.005 Gy or higher (mean dose of 0.2 Gy) appeared to be associated with radiation. The percentages attributable to radiation were 5.8%, 13%, 25%, 35% and 57% at dose ranges of 0.1–0.2, 0.2–0.5, 0.5–1, 1–2 and 2 Gy and higher (the person-year-weighted mean doses were 0.14, 0.31, 0.72, 1.4 and 2.5 Gy), respectively. The excess deaths for noncancer diseases were estimated as 353 (95% CI: −252, 958) using the ERR model with effect modifiers. About 1.8% (95% CI, −1.2%, 4.8%) among those with colon dose of 0.005 Gy or higher appeared to be associated with radiation. The value was 1.9% (95% CI, 1.2%, 2.7%) when the ERR model without effect modifiers was used because those effect modifiers were estimated less precisely due to small ERRs and high background rate.

DISCUSSION

The most important finding regarding the late effects of A-bomb radiation exposure on mortality is an increased risk of cancer mortality throughout life (*2*). The current data showed that the risk for all solid cancer deaths has continued to increase throughout the survivors' lifetimes in approximate proportion to radiation dose. The sex-averaged relative excess of solid cancer deaths was 42% per Gy at age 70 years after exposure at age 30 based on a linear

TABLE 6
Parameter Estimates of the Dose–Response Models for Excess Relative Risk (ERR) for all Solid Cancer in the Full Dose Range and for the Range of 0–2 Gy

	Full			<2 Gy		
Dose range model[a]	**L**[b]	LQ	Q	L	**LQ**	Q
β_1: linear	**0.42**	0.36	–	0.44	**0.22**	–
β_2: quadratic	**–**	0.038	0.22	–	**0.18**	0.33
Effect modification						
σ: sex (female = 1; male = −1)	**0.34**	0.35	0.40	0.28	**0.29**	0.29
τ: age at exposure (year)	**–0.035**	–0.034	–0.035	–0.033	**–0.034**	–0.035
υ: attained age (log(age/70))	**–0.86**	–0.86	–0.90	–0.84	**–0.89**	–0.97
Deviance	18301.2	18300.4	18324.9	17557.3	17551.6	17557.2
df	53147	53146	53147	49577	49576	49577
Test (vs. LQ model)	$P = 0.36$	–	$P < 0.001$	$P = 0.02$	**–**	$P = 0.02$

Note. Bolded columns are the selected models.

[a] The ERR model was defined as $\lambda_0(c,s,b,a)\,[1 + \rho(d) \cdot \exp(\tau\, e + \upsilon \ln(a)) \cdot (1 + \sigma\, s)]$, where d is colon dose, s is sex, b is birth year, e is age at exposure, and a is attained age. $\rho(d)$ was $\beta_1 d$ for the linear model, $\beta_1 d + \beta_2 d^2$ for the linear-quadratic model, and γd^2 for the quadratic model. τ, υ and σ are coefficients for effect modification.

[b] L: linear, LQ: linear-quadratic, Q: quadratic.

model with effect modification by age at exposure and attained age. The sex-averaged excess death rate of all solid cancer was 26/10,000 person-years per Gy under the same conditions. The second important finding is that those who were exposed at younger ages had a higher relative risk for cancer death; e.g., the sex-averaged ERR of solid cancer deaths was 0.83 at age 70 in those who were exposed at 10 years of age compared with 0.30 in those exposed at age 40. For solid cancers the relative risk declined with increasing attained age of the subjects as well as years after the bombing, although, importantly, the excess absolute rates continued to increase with attained age and the rates were higher in those exposed at younger ages among those with the same attained age. These findings suggest that young people are more sensitive to radiation than older people, possibly at the initiation stage in carcinogenesis at the time of exposure, and imply an overall increase in lifetime risk for those exposed at younger ages.

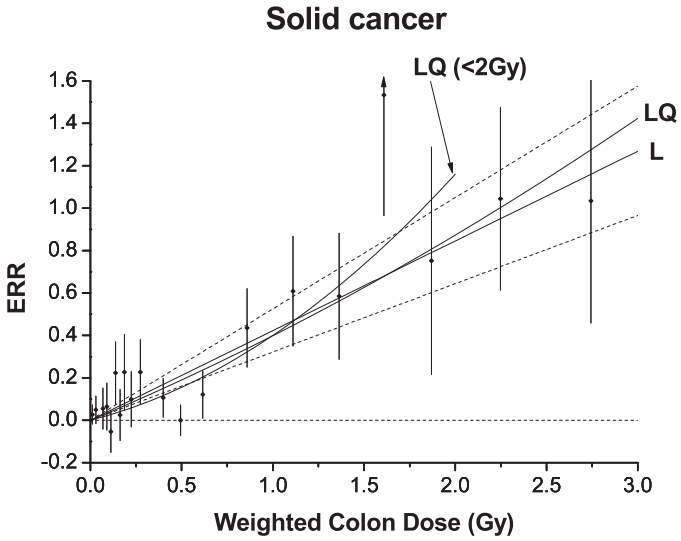

FIG. 4. Excess relative risk (ERR) for all solid cancer in relation to radiation exposure. The black circles represent ERR and 95% CI for the dose categories, together with trend estimates based on linear (L) with 95% CI (dotted lines) and linear-quadratic (LQ) models using the full dose range, and LQ model for the data restricted to dose <2 Gy.

To provide continuity, the methods of analysis and risk indicators are the same as those in previous reports since 1987 (*2, 10*). In a previous report, mortality data up to 2000 were examined for changes in the estimated risk of radiation due to changes in dosimetry between DS86 and DS02 (*4*). In that report the estimates of solid cancer risk per unit radiation dose decreased about 8% due to the upward revision in the γ-ray dose estimates (*4*). The ERR/Gy for all solid cancer decreased from 0.45 based on DS86 to 0.42 based on DS02 for 1950–2000 (*4*). The estimates of ERR/Gy and modifiers for solid cancer in this study (Table 4) were similar to those in the latter report (*4*). The effect-modification results showed substantially similar tendencies to previous estimates using DS86 and less follow-up time (*2,5*).

Effect modification was evaluated for the ERR (Table 4) and EAR (Table 5) models. The ERR estimates were

TABLE 7
Change in Dose–Response Curvature For Excess Relative Risk (ERR) of Solid Cancer in The range of 0–2.0 Gy by Observation Period

	1950–1985	1950–1995	1950–2003
Curvature (θ)[a]	0.20	0.40	0.81
95% CI[b]	(−0.23, 3.2)	(−0.09, 3.2)	(0.08, 8.6)
Significance (P)[c]	0.50	0.16	0.02

[a] The ERR model was defined as $\lambda_0(c,s,b,a)\,[1 + \beta_1(d + \theta d^2) \cdot \exp(\tau\, e + \upsilon \ln(a)) \cdot (1 + \sigma\, s)]$ separately for each period of analysis, where d is colon dose, s is sex, b is birth year, e is age at exposure, and a is attained age. τ, υ and σ are coefficients for effect modification.

[b] Confidence interval.

[c] Likelihood test.

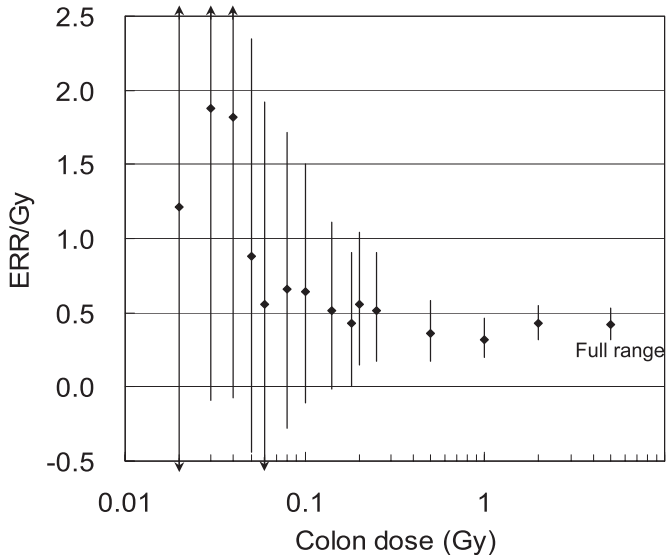

FIG. 5. Excess relative risk per Gy (ERR/Gy) for all solid cancer for selected dose ranges. The figure shows the ERR/Gy and 95% CI for a dose range from zero to a given dose based on the linear model for the full data that allowed for different ERRs below and above the given dose and taking radiation effect modifiers as common to the two dose ranges. The increased ERR/Gy in the low-dose levels less than 0.1 Gy corresponds to the estimates of ERR higher than the expected linear line in Fig. 4.

TABLE 8
Excess Relative Risk (ERR) Estimates per Gy for Noncancer Deaths, 1966–2003

Cause of death	Number of deaths	ERR/Gy[a]	(95% CI[b])	*P*
Noncancer disease[c]	25,618	0.13	(0.08, 0.18)	<0.001
Circulatory disease	14,586	0.11	(0.05, 0.18)	<0.001
Respiratory disease	4,190	0.23	(0.11, 0.36)	<0.001
Digestive disease	2,226	0.20	(0.05, 0.38)	0.009
Genitourinary disease	951	0.18	(−0.06, 0.46)	0.15
Infectious disease	781	–0.03	(−0.22, 0.23)	>0.5
Other disease	2,884	0.03	(−0.11, 0.19)	>0.5

[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.
[c] Non-neoplastic blood diseases were excluded from noncancer diseases.

substantially higher for women than men, but the EAR estimates were not. This appears to be a function of the fact that the background mortality rates of cancer were substantially higher in men than in women in this cohort. Similarly, it was observed that cancers having a low background mortality rate tend to have a relatively high ERR, and vice versa. The gender similarity in EAR estimates suggests that the excess of deaths due to radiation is mostly constant in rate rather than in ratio (i.e., more additive than multiplicative) to the background cancer rates. This interpretation is consistent with the differences in ERR between sites of cancer mentioned above.

Age at exposure is an important modifying factor in radiation-induced carcinogenesis. Both the ERR and the EAR were higher for younger ages at exposure (Tables 4 and 5, Figs. 2 and 3). However, other reports [for example, the BEIR VII and UNSCEAR 2006 Reports (*6, 23*)] have indicated that the ERRs for those exposed at age 60 years or older were similar to or higher than risks for those exposed at age 40 or 50 years, especially for cancer incidence data (*5, 21, 22*). The nonparametric category-specific estimates of age-at-exposure effects on all solid cancer mortality risk in the current study were similar to the corresponding figures reported by Walsh (*22*), in which an increased risk at an old age at exposure was less remarkable than in the figure reported by Preston *et al.* (*5*).

The linear dose–response relationship provided the best fit to the solid cancer data across the entire dose range in this study, but significant upward curvature was observed over the truncated dose range of 0–2 Gy (Table 7), which had been hinted at in previous reports (*4, 5*). DDREF is defined by dividing the slope of a nonlinear function at low-dose levels by the slope of the extrapolated linear nonthreshold function based on the whole dose range (*23*), so that this upward curvature may imply a DDREF greater than one. However, the dose–response slope was nominally higher at doses below 0.1 Gy than it was overall or for the dose range 0–2 Gy (Fig. 5). The apparent upward curvature appears to be related to relatively lower than expected risks in the dose range 0.3–0.7 Gy (Fig. 4), a finding without a current explanation. A recent paper (*24*) compared the risk of cancer mortality and incidence in 12 studies of low-dose-rate, moderate-dose exposure (mostly external) with those values in the LSS. The ERR per dose for each study was calculated using the same gender distribution, average age at exposure, and average attained age as in the LSS. The expected DDREF based on the ratio of ERR per dose in those studies to that in the LSS appeared to be close to 1.0, nominally lower than the factors suggested by BEIR VII (1.5) (*23*) and ICRP (2.0) (*25*). However, the number of examined studies was limited to the publication period of 2002–2007 with conditions allowing calculation of the values matching the LSS (*24*), so the arguments are still controversial.

The high risks per unit dose observed in the low-dose range are difficult to interpret. One suggestion was that cumulative exposures to diagnostic medical radiation over the many years of follow-up may have reached a considerable proportion of the estimated individual A-bomb doses at the low-dose levels (*26*). However, to impact the ERR estimates, medical exposures or other sources of exposure, including fallout and residual radiation, would have to have preferentially exposed subjects with very low doses. In the LSS, zero-dose subjects were located at around 4 km or farther from the hypocenter while the subjects with doses of up to 50 mGy were located around the range of 2 to

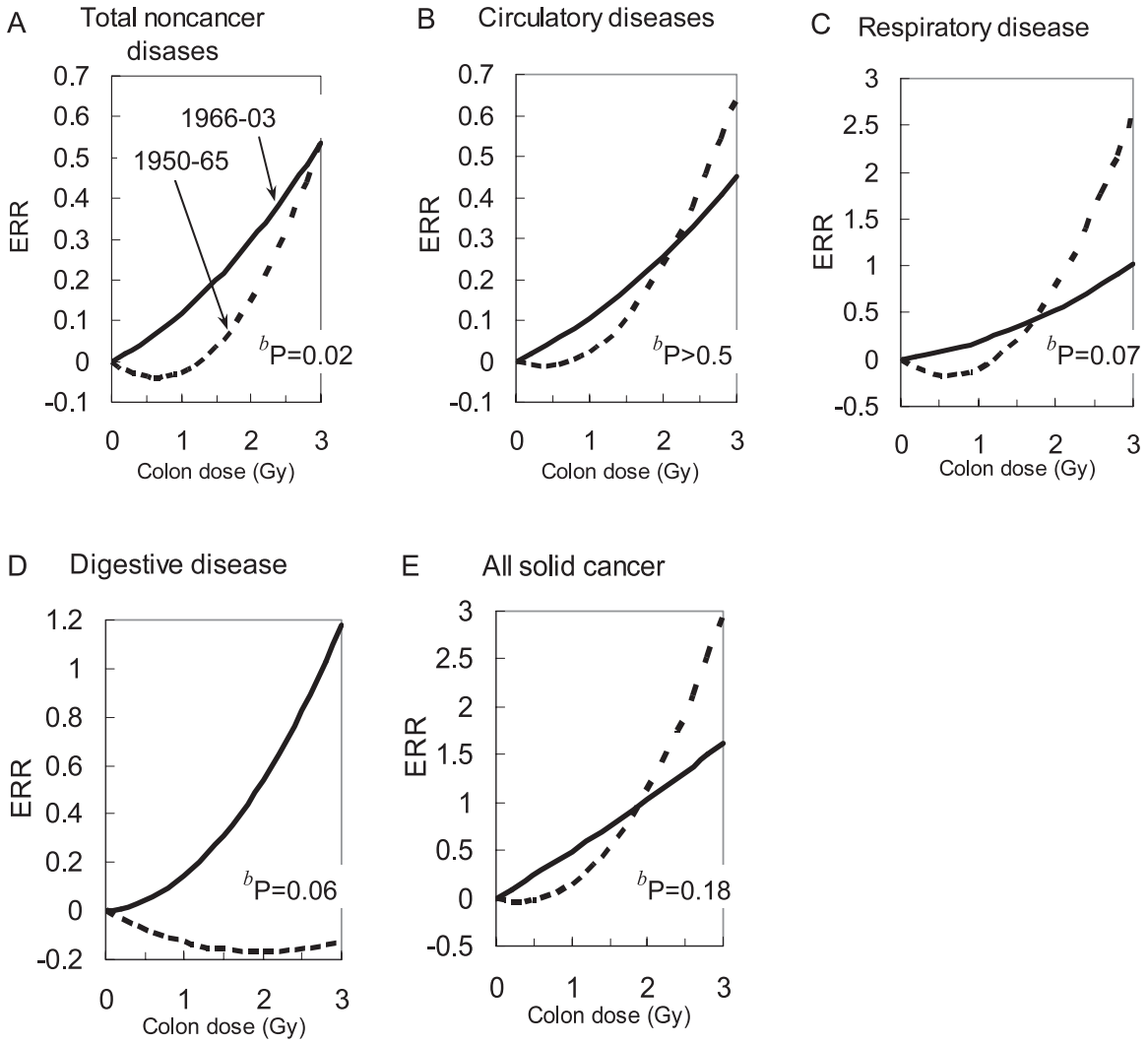

FIG. 6. Comparison of dose–response curve[a] for early period (1950–1965, shown with dashed line) and for late period (1966–2003, shown with solid line) from noncancer diseases (based on LQ without any effect modification) and all solid cancer (based on LQ with effect modifications). [a]Based on the ERR model defined as the linear-quadratic model without effect modifications for noncancer diseases: $\lambda 0(c,s,e,a)$ [1 + $\beta_1(d + \theta d^2)$], and the model with effect modifications for all solid cancer: $\lambda 0(c,s,e,a)$ [1 + $\beta_1(d + \theta d^2) \cdot \exp(\tau\, e + \upsilon \ln(a)) \cdot (1 + s\, s)$], where d is colon dose, s is sex, e is age at exposure, and a is attained age. The figure for all solid cancer shows the sex-averaged estimates for $e = 30$ years and $a = 70$ years. [b]Significance of the difference between the two curves.

TABLE 9
Observed and Excess Deaths from Solid Cancer and Noncancer Diseases

			Solid cancer			Noncancer diseases[b]		
Colon dose (Gy)	Number of subjects	Person-years	Number of deaths	Number of excess cases[a]	Attributable fraction (%)	Number of deaths	Number of excess cases[b]	Attributable fraction (%)
<0.005	38,509	1,465,240	4,621	2	0	15,906	1	0
0.005–	29,961	1,143,900	3,653	49	1.3	12,304	36	0.3
0.1–	5,974	226,914	789	46	5.8	2,504	36	1.4
0.2–	6,356	239,273	870	109	12.5	2,736	82	3.0
0.5–	3,424	129,333	519	128	24.7	1,357	86	6.3
1–	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] Based on the ERR model was defined as the linear model with effect modification: $\lambda_0(c,s,b,a)[1 + \beta_1 d \cdot \exp(\tau\, e + \upsilon \ln(a)) \cdot (1 + \sigma\, s)]$.
[b] Non-neoplastic blood diseases were excluded from noncancer diseases.

4 km. Thus, with such a large geographical distribution, differential exposures to additional radiation sources seem implausible, although we have insufficient information about fallout or residual radiation to completely rule out this possibility.

Potential causes other than radiation include selection bias due to early mortality prior to study initiation in a manner that correlates with dose (e.g., high doses among urban people and lower doses among rather rural people) (*1, 2, 5, 27, 28*). Suggestively lower baseline mortality has been shown in the low-dose but relatively proximal survivors compared to the more distant survivors, which suggests that sociodemographic factors such as urban-rural differences may be more important than dose-based selection effects (*1, 2, 27, 28*). However, sociodemographic selection effects might have weakened because of modernization of the Japanese lifestyle over the decades. The issues related to the influences of dose, latency and sociodemographic-lifestyle factors on mortality from noncancer diseases in the LSS require further investigation.

A variety of studies of risks for site-specific cancers from external exposure to low-LET (linear energy transfer) radiation are documented in the UNSCEAR 2006 Report (*6*). Most studies were based on either subjects with high-dose radiation such as radiotherapy or radiation workers with low-level exposures. Thus the LSS is often thought to provide the most reliable estimates of radiation effects because of its large size, wide range of relatively precise individual doses, observation of numerous diseases, and long follow-up period. Cancers of the esophagus, stomach, colon, lung, breast, ovary and bladder and transitional cell carcinoma of kidney, pelvis and ureter are thought to be associated with low- and high-dose radiation based on the LSS and other studies (*6*). A strong interaction between radiation and smoking was observed in the risk of lung cancer (*29*), so high ERRs of smoking-related cancers might be partly due to such an interaction. Rectal cancer is thought to be inducible after high-dose radiotherapy exposures (*6*), but no association has been observed among the LSS. On the other hand, an association of liver cancer with radiation exposure has not been demonstrated in studies of medical and occupational exposure to low-LET radiation, while the LSS showed a significant increase in risk (*6*). It is inconclusive whether there was a synergism between HCV infection and radiation (*30*) or independent effects by each of them (*31*). Cancers of the pancreas, prostate and uterine cervix are not thought to be associated with radiation (*6*), which is consistent with the results of this study. Uterine corpus and kidney parenchymal cancers are possibly associated with a high-dose radiation exposure (*6*), but this association was not observed in this study.

Most excess cases of leukemia occurred shortly after the atomic bombings, even before the beginning of the LSS (*32*), and a modestly elevated risk has continued at a low level over the last several decades (*1, 7*). In this study, the estimated ERR at 1 Gy for total leukemia was 3.1 (95% CI: 1.8, 4.3) using a linear-quadratic model without effect modification, based on 313 cases, which is similar to a recent, more detailed leukemia report (*7*). An analysis of malignant lymphoma mortality in the LSS was conducted recently based on the subset of males of working age at the time of the bombing (*33*). The present study similarly found an excess for males [ERR/Gy of 0.70 ($P = 0.02$)] but no association for women [ERR/Gy $= -0.18$ ($P = 0.33$)]. We have no explanation for the disparity between the male and female results and believe the radiation effect should be interpreted cautiously due to both the gender disparity and the diversity of malignancies under the rubric of lymphoma. Earlier LSS reports of multiple myeloma mortality (*34*) did not show statistically significant excesses. But, based on hematologically reviewed incident cases from leukemia registries and tumor registries, Preston *et al.* (*35*) showed an ERR/Gy $= 0.25$ ($P > 0.5$) based on 30 first primary cases with shielded kerma under 4 Gy and ERR/Gy $= 0.9$ ($P = 0.02$) after adding seven cases of second primaries and those with shielded kerma >4 Gy. In the present study (all with bone marrow doses ≤ 4 Gy), ERR/Gy of multiple myeloma was 0.11 ($P > 0.5$) in males and 0.86 ($P = 0.04$) in females based on 34 and 59 cases, respectively.

In this overview, risk of noncancer diseases was reported using a broad classification of disease types. The elevated risk of diseases of the blood and blood-forming organs may be genuinely due to the effects of radiation or to possible misdiagnoses of hematopoietic malignancies as non-neoplastic conditions, since many death certificates were completed without intensive investigations as to the cause of death (*8*). The risk of circulatory diseases was significantly higher. This is important because circulatory diseases are the leading cause of death in developed countries (*6*); detailed results for circulatory disease deaths among the LSS have been reported elsewhere (*36*). The risk of respiratory diseases was also significantly elevated due to the increased risk of pneumonia and influenza, which constituted 63% of the deaths from respiratory diseases. However, characteristics of pneumonia and influenza appeared to be different between the periods of observation; namely, it was associated with acute epidemics in the early period but was more likely to be associated with terminal diseases among the elderly in the more recent period. Hence a problem in interpreting pneumonia and influenza deaths is that they may be associated with other concurrent or underlying diseases. Although digestive diseases showed an association with radiation during 1966–2003, liver cirrhosis, which constituted 43% of digestive disease deaths during that period, did not show any increased radiation risk. Therefore, further detailed analyses of both respiratory and digestive diseases are planned. There was no association of radiation dose and death due to external causes or to infectious/parasitic diseases.

The strengths of this LSS mortality study are, as stated previously (*2, 4, 34*), (1) a large, representative sample across all age groups of A-bomb survivors who were alive

in 1950, using stratified sampling to enrich the higher-dose portion of the sample, (2) reasonably precise estimates of individual doses, (3) a wide range of doses in the cohort, (4) complete ascertainment of mortality and cause of death using the *koseki* system, and (5) a long observation period with a large number of deaths. Those strengths provide a high-quality, informative epidemiological study.

A potential limitation of the LSS was that the subjects were the ''survivors'' of physical injuries and burns from the A-bomb explosion and biological injuries due to deterministic radiation effects. Additional stressors included poor nutrition and bad hygienic conditions in Japan in the postwar period. Those conditions might have led to early mortality and hence selective exclusion of vulnerable people, including vulnerability to radiation, from the available subjects in 1950. Nevertheless, the stochastic late health effects such as cancer development are not likely to be affected by such selection bias, which is supported by the negligible discrepancies in the dose–response curves between the early and late periods for all solid cancer (Fig. 6). A careful analysis of this phenomenon would require breakdowns by period, cancer site and other factors. Another unavoidable exclusion is that perhaps an appreciable number of leukemia cases occurring before 1950 were lost to the study (*32*). On the other hand, the significant discrepancy between the early and late calendar periods for noncancer diseases ($P = 0.02$) implies a potential selection bias for noncancer diseases as a whole. The discrepancy was not observed in circulatory diseases, while borderline differential patterns were observed for respiratory and digestive diseases. More detailed analyses are required.

In conclusion, the risk of death from malignant neoplasms in most sites and selected noncancer diseases increased in a dose-dependent fashion among LSS subjects over the period 1950–2003. The relative risk of radiation for solid cancer was largest among those exposed at young ages. The results of this study, which extended the observations for 6 years, are consistent with previous reports and continue to show increased cancer risks throughout the survivors' lifetimes. Since epidemiological evaluation can be done only after the development of outcomes, we sincerely pay our respects to those who have died. It would be our pleasure if clarification of late health effects of A-bomb radiation could offer fundamental information for the survivors' welfare. Clearly the LSS will continue to provide increased precision in risk estimation and additional information regarding risk modification by other factors, as 42% of the survivors in LSS subjects overall, and 80% of those who were exposed to radiation at the age of 20 years or younger, were still alive at the end of follow-up in 2003.

ACKNOWLEDGMENTS

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through DOE Award DE-HS00000031 to the National Academy of Sciences. This publication was supported by RERF Research Protocol RP 1–75. The views of the authors do not necessarily reflect those of the two governments.

Received: March 23, 2011; accepted: November 28, 2011; published online: December 15, 2011

REFERENCES

1. Beebe GW, Ishida M, Jablon S. Studies of the mortality of A-bomb survivors. 1. Plan of study and mortality in the medical subsample (Selection 1), 1950–1958. Radiat Res 1962; 16:253–80.
2. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003; 160:381–407.
3. Young R, Bennett B, editors. DS02: A revised system for atomic bomb survivor dose estimation. Hiroshima: Radiation Effects Research Foundation; 2006.
4. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, et al. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res 2004; 162:377–89.
5. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007; 168:1–64.
6. United Nations Scientific Committee on the Effects of Atomic Radiation. Effects of ionizing radiation. UNSCEAR 2006 Report, Volume 1. New York: United Nations; 2008.
7. Richardson D, Sugiyama H, Nishi N, Sakata R, Shimizu Y, Grant E, et al. Ionizing radiation and leukemia mortality among Japanese atomic bomb survivors, 1950–2000. Radiat Res 2009; 172:368–82.
8. Beebe GW, Kato H, Land CE. Studies of the mortality of A-bomb survivors. 6. Mortality and radiation dose, 1950–1974. Radiat Res 1978; 75:138–201.
9. Kato H, Johnson KG, Yano K. Mail survey on cardiovascular disease study, Hiroshima-Nagasaki. ABCC TR 19-66. Hiroshima: Atomic Bomb Casualty Commission; 1966.
10. Preston DL, Kato H, Kopecky KJ, Fujita S. Studies of the mortality of A-bomb survivors. 8. Cancer mortality, 1950–1982. Radiat Res 1987; 111:151–78.
11. Cullings HM, Fujita S, Funamoto S, Grant EJ, Kerr GD, Preston DL. Dose estimation for atomic bomb survivor studies: Its evolution and present status. Radiat Res 2006; 166:219–54.
12. Manual of the international statistical classification of diseases, injuries and causes of death: 7th revision (ICD-7). Geneva: WHO; 1957.
13. International classification of diseases, revision 8 (ICD-8). Geneva: WHO; 1967.
14. International classification of diseases, ninth revision (ICD-9). Geneva: WHO; 1977.
15. International classification of diseases, tenth revision (ICD-10). Geneva: WHO; 1993.
16. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor studies: Its evolution and present status. Radiat Res 1990; 123:275–84.
17. Breslow NE, Day NE. Statistical methods in cancer research, Vol. II. The design and analysis of cohort studies. IARC Scientific Publications No. 83. Lyon: International Agency for Research on Cancer; 1988.
18. Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part II. Noncancer mortality: 1950–1990. Radiat Res 1999; 152:374–89.
19. Preston DL, Lubin JH, Pierce DA, McConney ME. Epicure users guide. Seattle: Hirosoft International Corporation; 1993.

20. Akaike H. A new look at statistical model identification. IEEE Trans Automat Control 1974; 19:716–23.

21. Little MP. Heterogeneity of variation of relative risk by age at exposure in the Japanese atomic bomb survivors. Radiat Environ Biophys 2009; 48:253–62.

22. Walsh L. Heterogeniety of variation of relative risk by age at exposure in the Japanese atomic bomb survivors. Radiat Environ Biophys 2009; 48:345–7.

23. National Research Council, Committee on the Biological Effects of Radiation. Health risks from exposure to low levels of ionizing radiation (BEIR VII Phase 2). Washington, DC: National Academies Press; 2006.

24. Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H. Is cancer risk of radiation workers larger than expected? Occup Environ Med 2009; 66:789–96.

25. The 2007 recommendations of the ICRP – Publication 103. Annex A. Biological and epidemiological information on health risks attributable to ionising radiation. Ann ICRP 2007; 37:137–246.

26. Yamamoto O, Antoku S, Russell WJ, Fujita S, Sawada S. Medical X-ray exposure doses as possible contaminants of atomic bomb doses. TR 16–86. Hiroshima: Radiation Effects Research Foundation; 1986.

27. Cologne JB, Preston DL. Longevity of atomic-bomb survivors. Lancet 2000; 356:303–7.

28. Cologne JB, Preston DL. Impact of comparison group on cohort dose response regression: an example using risk estimation in atomic-bomb survivors. Health Phys 2001; 80:491–6.

29. Furukawa K, Preston DL, Lönn S, Funamoto S, Yonehara S, Matsuo T, et al. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. Radiat Res 2010; 174:72–82.

30. Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S, et al. Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. Int J Cancer 2003; 103:531–7.

31. Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, et al. Impact of radiation and hepatitis virus infection on risk of hepatocellular carcinoma. Hepatology 2011; 53:1237–45.

32. Folley JH, Borges W, Yamawaki T. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. Am J Med 1952; 13:311–21.

33. Richardson D, Sugiyama H, Wing S, Sakata R, Grant EJ, Shimizu Y, et al. Positive associations between ionizing radiation and lymphoma mortality among men. Am J Epidemiol 2009; 169:969–76.

34. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. Radiat Res 1996; 146:1–27.

35. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 1994; 137 Suppl:S68–97.

36. Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ 2010; 340:b5349.

APPENDIX
Classification of Cause of Death in This Report

	Edition of International Classification of Diseases (ICD) and applicable years			
	ICD-7 1950–1968	ICD-8 1969–1978	ICD-9 1979–1997	ICD-10 1998–2003
Neoplasm	140–205, 210–239, *251*	140–239	140–239	C00–C97
All solid cancer	140–199	140–199	140–199	C00–C80
Esophagus	150	150	150	C15
Stomach	151	151	151	C16
Colon	153	153	153	C18
Rectum	154	154	154	C19–C20
Liver	155 (0, 8), 156	155, 197.8	155 (0, 1, 2)	C22 (0–4, 7, 9)
Gallbladder	155.1	156	156	C23, C24
Pancreas	157	157	157	C25
Other digestive system	158, 159	158,159	158,159	C26, C48
Lung	162 (0, 1, 8), 163	162	162	C33, C34
Breast	170	174	174,175	C50
Uterus	171, 172, 174	180, 182.0, 182 (9)	179–180, 182	C53, C54, C55.9
Ovary	175	183	183	C56, C57 (0, 1, 2, 3, 4)
Prostate	177	185	185	C61
Bladder	181	188	188	C67
Kidney parenchyma	180	189	189	C64
Renal pelvis, other urinary tract	180	189 (1, 2)	189 (1, 2)	C65, C66
Other solid cancer	Others in 140–199	Others in 140–199	Others in 140–199	Others in C00–C80
Leukemia	204	204–207	204–208	C91 (0–3, 5, 7, 9), C92 (0–5, 7, 9), C93, C94 (0–3, 7), C95
Malignant lymphoma	200–202, 205	200–202	200–202	C81–C85, C91.4, C96
Multiple myeloma	203	203	203	C88. (7, 9), C90
Other neoplasms	210–239, 251	208, 210–239	210–239	C94.4, D00–D48, Q85.0
Non-neoplastic diseases				
Blood disease	290–299, 468 (0, 1, 2)	209, 280–289	280–289	D50–D75, D77, C94.5
Circulatory disease	330–334, 400–467, 468.3	390–458	390–459	I00–I99, G45, M30
Respiratory disease	240–241, 470–527	460–519	460–519	J00–J64, J66–J99, R09.1
Pneumonia and influenza	480–493	470–486	480–487	J10–J18
Digestive disease	530–587	520–571	520–571	K00–K92
Liver cirrhosis	581	571	571	K70, K73, K74
Genitourinary disease (*additional for female)	590–617, 620–637*	580–607, 610–629*	580–608, 610–629*	N00–N50, N60–N98*
Infectious Disease	001–138	000–136	001–139	A00–A32, A35–B99, D86, J65, M35.2
External causes	N800–N999	N800–N999	800–999	S00–T98