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Mortality Analysis of the Life Span Study (LSS) Cohort Taking into Account Multiple Causes of Death Indicated in Death Certificates

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Mortality analyses have been performed using underlying causes of death as reported on death certificates; these are uniquely determined for a deceased person according to the World Health Organization coding system. Comorbidities, the disease conditions other than the underlying cause of death from death certificates recording multiple causes of death, have rarely been explored in Life Span Study subjects. The purpose of this study was to clarify associations between atomic bomb radiation exposure and mortality from combinations of the underlying cause of death and comorbidities. The focused follow-up period was 1977–2003, prior to which death certificate accuracy was unreliable. The study cohort was comprised of 10,017 people for whom the category "all circulatory disease" was listed as the underlying cause of death, of which heart disease (rheumatic, hypertensive and ischemic heart disease) and stroke were major subtypes. Comorbidities considered were pneumonia, renal disease, diabetes mellitus, cancer and the major circulatory disease subtypes listed above. Poisson regression models were used for analyses. Excess relative risks (ERRs) for mortality at 1 Gy were significantly increased when cancer was comorbid with all circulatory disease, heart disease, ischemic heart disease or stroke, ranging from 0.61 [95% confidence interval (CI): 0.13, 1.41; N = 177] for all circulatory diseases to 1.60 (CI: 0.07, 4.86; N = 42) for ischemic heart disease. Among the other comorbidities, only diabetes comorbid with heart disease had a significant radiation dose response (ERR at 1 Gy of 0.62, CI: 0.10, 1.46; N = 128). It remains uncertain if the high ERRs with comorbid cancers were anomalous due to the small number of cases or some dissimilarity in statistical methodologies, or if this might suggest some pathogenetic basis for increased fatality. For this reason, further investigation is required.

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INTRODUCTION

Follow-up studies of atomic bomb survivors have been undertaken to investigate the health effects of exposure to atomic bomb radiation. The knowledge obtained from these studies has been useful for managing health administration, improving quality of life for survivors, understanding medical mechanisms of radiation-induced diseases and formulating radiation protection standards, as recommended by the International Commission on Radiological Protection (ICRP). A cohort study concerning mortality of the survivors, the Life Span Study (LSS), has been ongoing since 1950 by the Atomic Bomb Casualty Commission (ABCC) and by ABCC's successor organization, the Radiation Effects Research Foundation (RERF). In the LSS, vital statistics are obtained through the Japanese National Family Registration (koseki) system and causes of death are obtained from death certificates (*1, 2*).

Mortality analyses have been performed using underlying cause of death coded according to the International Classification of Diseases (ICD) and the coding system recommended by World Health Organization (WHO) (*3*). Underlying cause of death is uniquely determined for a deceased person by use of WHO selection rules. WHO defines the underlying cause of death as ''the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury''. (*3*) This current method of selecting a single disease or injury as the underlying cause of death has many advantages, including assurance of compatible mortality statistics among various countries (*4*). To ensure continued compatibility and high-quality classification, the system has been updated over the years. Each ICD revision has made it more feasible to precisely identify many varieties or sites of diseases and injuries (*3*). In this text, the seventh, eighth, ninth and tenth revisions of the ICD are used according to the ICD system in place when each death occurred. Often, although two or more important diseases or conditions are thought to have led to death and are listed on the death certificate, only one cause of death is coded as the underlying cause of death.

Causes of death other than the underlying cause of death are known in this article as ''comorbidities''.

Overall, there are few published comorbidity studies in Japan. Ueda (*5*), reported that hypertension was found to be the most likely comorbidity listed when stroke was the underlying cause of death and believed that a single cause of death was not sufficient to understand the true pathogeneses of death. Umeda *et al*. (*6*) found that heart disease and pneumonia were likely to be listed as comorbidities when the underlying cause of death was stroke and *vice versa* with stroke, when heart disease was the underlying cause of death.

With the exception of Ishida *et al*. (*4*) and Shimizu *et al*. (*7*), there are no published comorbidity studies of the LSS cohort. Ishida *et al*. (*4*) investigated the frequency of comorbidities and found a paucity of available data over the follow-up period of 1950–1959, and he reiterated the importance of utilizing all available information, including comorbidities. Shimizu *et al*. (*7*) indicated that radiation risk estimates on the basis of both underlying and contributing cause of death combined together were nominally higher than those based on underlying cause of death alone. With the recent increase in deaths from chronic diseases and advances in medical technology, multiple important diseases and conditions associated with death have become more likely to be listed together on death certificates; thus, a study of comorbidities will provide a broader range of information for analysis of mortality in the atomic bomb survivors.

The goal of this study was to elucidate the association between atomic bomb radiation exposure and mortality from combinations of underlying causes of death and comorbidities using the death certificates from the LSS cohort. We hypothesized that radiation plays a role in certain major underlying causes of death that are further related to specific comorbidities, with risk that might be heterogeneous, i.e., differ from the overall risk for the underlying cause of death disregarding comorbidities. Because circulatory disease is a major cause of death among the Japanese population (*8*), this study focused on individuals with all circulatory disease listed as the underlying cause of death.

MATERIALS AND METHODS

Underlying Cause of Death and Comorbidities

The current study targeted those individuals for whom all circulatory disease was considered the underlying cause of death. Here, diagnosis of all circulatory disease is defined as having at least one of the following: heart disease, stroke or other circulatory disease. Since discussion regarding combinations with comorbidities requires a clear pathogenetic basis, heart disease in this study is further divided into three subtypes: rheumatic heart disease, hypertensive heart disease and ischemic heart disease. Heart failure has been a very common diagnosis on death certificates in Japan as it was used in the past to denote ill-defined or unknown pathogenetic processes. Since it frequently refers to nonspecific circulatory diagnoses, in this study, the diagnosis ''other circulatory disease'' (of which heart failure constitutes the majority) was included in the category ''all circulatory disease'', but not in ''heart disease''. Classification of the diseases used in this study and the ICD revisions applicable are shown in Appendix Table A1.

A Japanese death certificate includes several columns for causes of death and related conditions. Column I includes multiple boxes labeled (a) to (c) or (a) to (d), depending on the revision. The diseases or conditions that led directly to death are listed in order of relevance to the death in these boxes. The underlying cause of death is usually selected from the bottom-most entry. Column II includes all other significant diseases or conditions contributing to death but not relating directly to it. There are also additional columns reserved for findings during surgeries and/or autopsy, respectively, if these procedures were performed.

For this study, comorbidities were selected from all disease conditions listed in any of the columns. Each was classified and placed into one of following categories: pneumonia, renal disease, diabetes mellitus and cancer. Other major categories of circulatory disease were also considered, provided they did not overlap the underlying cause of death. Comorbidities were selected based on previously noted associations with radiation exposure and clinical significance, as explained below. Pneumonia is a dominant subtype of respiratory disease and has been the third leading cause of death in Japan since 2011 (*8*). Furthermore, respiratory disorders are associated with cardiac load, as the lungs are the site of blood oxygenation during pulmonary circulation. An association between radiation exposure and mortality from respiratory disease has been observed in the LSS (*9*). Renal disorders are known to induce renal hypertension and impair cardiac function (*10*), an association that has been observed among the survivors (*11*). An association between atomic bomb radiation exposure and renal mortality has also been observed (*12*). Diabetes mellitus is one of the most important risk factors of circulatory disease (*13, 14*). An association between high levels of radiation exposure to the pancreas and risk of subsequent diabetes diagnosis has been observed among childhood cancer survivors (*15*), but not among the atomic bomb survivors, who received relatively lower doses. Cancer is a major cause of death in the Japanese Vital Statistics (*8*), since each subtype of all circulatory disease is counted for tabulations respectively in it, and cancer is also definitively associated with radiation exposure in the LSS (*1, 2*). Therefore, these four common comorbidities, pneumonia, renal disease, diabetes mellitus, cancer, as well as major categories of circulatory disease (in addition to their role as the underlying cause of death) were selected as comorbidities for analysis in this study.

Combinations of underlying cause of death and comorbidities were not mutually exclusive, i.e., a case with several comorbidities was counted multiple times. Since the number of cases from each exclusive combination is small, statistical power from a detailed mutually exclusive classification system would be inadequate for a meaningful interpretation of results. Also, defining clinical criteria to determine exclusive conditions was impractical since too many conditions overlap with one another.

Subjects and Follow-Up Period

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 a similarly sized group of age- and sex-matched survivors who were between 2.5 and 10 km from the hypocenters (*1, 2*). This study comprised 86,611 LSS cohort members whose individual weighted absorbed colon dose (Gy) had been estimated by Dosimetry System 2002 (DS02) (*16, 17*), with random measurement errors in these dose estimates adjusted by using the method proposed by Pierce *et al*. (*18*). Mortality follow-up and cause of death were investigated using the koseki system and death certificates. In this study, we used information on city, sex, birth year, death year, radiation dose, underlying causes of death and comorbidities. The weighted absorbed colon dose was calculated as the gamma ray dose plus 10 times the neutron dose for these analyses.

Since cardiovascular disorders are considered multifactorial systemic processes involving multiple internal organs, colon dose is used, which is consistent with past RERF reports (*1, 2, 7, 19*).

Counts of injuries and disease conditions on death certificates varied over the full follow-up period between 1950 and 2003. Prior to 1977, 59% of 9,035 death certificates listed all circulatory disease as the underlying cause of death with at least one additional injury or disease condition; only 4% of these death certificates had four or more injuries or disease conditions listed. After 1977, these values increase to 66% and 12%, respectively, of 10,017 deaths (data not shown). In addition to the increase seen in the number of death certificates with multiple listed injuries and/or disease conditions, an improvement in the reliability of diagnoses on death certificates also likely occurred after 1977 for several specific reasons. First, the proportion of people who died in hospitals rather than at home or other locations exceeded 50% throughout Japan in that year (*8*). Since agreement between clinical diagnoses on death certificates and autopsy diagnoses is generally better for deaths that occur in hospitals than for deaths outside hospitals (*20*), agreement is likely to have improved. Furthermore, computed tomography (CT) scanning was introduced into medical practice in Japan in the late 1970s, improving clinical diagnoses.

In addition, around 1977, the ICD was updated from the 8th to the 9th revision. Given the substantial improvement in identifying comorbidities beginning in 1977, the main analyses discussed here focuses on the observation period of 1977–2003. Subsequent analyses of the prior period (1950–1976) were also performed for comparison.

Statistical Methods

Poisson regression methods were used to evaluate the relationship between radiation exposure and mortality from combinations of underlying causes and comorbidities. For the analyses, the number of deaths and person-years were tabulated in strata cross-classified by city, sex, colon dose (20 categories with the following cut-points: 0, 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, 1.25, 1.5, 1.75 and 2 Gy), attained age (17 categories at five-year intervals from age 0–84, and 85 or older), age at exposure = 1945 – birth year (15 categories at five-year intervals from age 0–69, and 70 or older), proximal distance from the hypocenters (within 3 km or 3–10 km) and follow-up period (18 categories at three-year intervals from 1950 to 2003). Each stratum contains cause-specific counts of the number of deaths and person-years along with person-year weighted mean values of weighted colon dose, attained age and age at exposure, as is conventional in the LSS study (*1, 2, 7, 21*).

When Y_i is the number of deaths from a given underlying cause of death or a given combination of underlying cause of death and comorbidities for the ith cross-classified stratum, Y_i's are assumed to be independent Poisson random variables with the expectation values $E(Y_i) = n_i\,\lambda_i$, where n_i is person-years and λ_i is mortality for the ith stratum. The mortality λ_i was modeled using a relative risk-type function, and the parameters in the function were estimated using the maximum likelihood method:

$$\lambda_i(d_i) = \lambda_0(c_i, s_i, a_i, b_i, p_i)[1 + \rho(d_i)], \tag{1}$$

where λ_0 is the baseline, or background mortality of the ith stratum depending on city (c_i), sex (s_i), attained age (a_i), birth year (b_i) and proximal distance category (p_i). The baseline model was based on the models by Preston *et al.* (*1*). The dose-response $\rho(d)$ is the ERR model defined by linear, quadratic and linear-quadratic models, which were considered in order of simplicity:

$$\text{Linear model: } \rho(d) = \beta_1 d \tag{2}$$

$$\text{Quadratic model: } \rho(d) = \beta_2 d^2 \tag{3}$$

$$\text{Linear-quadratic model: } \rho(d) = \beta_1 d + \beta_2 d^2 \tag{4}$$

The best model among the three was selected based on Akaike information criterion (AIC) values (*22, 23*), but the simpler model was selected when the difference in AIC values was within 1.00 (*21, 24, 25*).

Excess relative risk at 1 Gy for the ith stratum is estimated by the parameters β_1, β_2 and $\beta_1 + \beta_2$ according to the above models (2), (3) and (4), respectively. In the current study, dose-response analysis for the combination of underlying cause and comorbidities was performed when the number of subjects with a given combination was 40 or more in the period from 1977–2003.

SAS version 9.3 (SAS Institute Inc., Cary, NC) and Epicure (HiroSoft International Corp., Seattle, WA) (*26*) software were used for the analyses in this study. Significance tests and 95% confidence intervals were based on X^2 approximations to the distribution of likelihood ratio tests (*1*). All two-sided P values <0.05 were considered statistically significant.

RESULTS

Number of Deaths with Comorbidities

Table 1 shows the number of deceased individuals with all circulatory disease listed as the underlying cause of death with at least one comorbidity for the two periods, 1950–1976 and 1977–2003. In the period 1977–2003, 41% of all circulatory disease deaths included at least one comorbidity. This percentage is likely low compared to that of the individual subtypes; the all circulatory disease category includes multiple subtypes such as heart disease, stroke and other circulatory disease (including heart failure). Due to the overlap it would cause, these subtypes are not considered comorbidities of all circulatory disease even if more than one is listed. To be considered a comorbidity of the catch-all category of all circulatory disease, the accompanying disease is required to be noncirculatory in nature (e.g., cancer, renal disease, diabetes and pneumonia). On the other hand, if subtypes of all circulatory disease are listed as the underlying cause of death, other types of circulatory disease can be listed as comorbidities. Consequently, the percentage of deaths with comorbidities is higher when tabulated by specific subtypes. For heart disease, 74–95% of death certificates included at least one comorbidity, while for stroke, 64% of death certificates included at least one comorbidity. For other circulatory disease, the number was less than 50%.

Table 2 shows the number of deceased subjects with combinations of underlying cause of death and targeted comorbidities in the two periods (allowing for combinations of underlying cause of death and comorbidities to be counted more than once). Among the 10,017 subjects who had all circulatory disease listed as their underlying cause of death in the period from 1977–2003, a total of 956 had pneumonia as a comorbidity, 469 had renal disease, 306 had diabetes and 177 had cancer. For those who had heart disease listed as their underlying cause of death, stroke was the most common comorbidity (345 subjects). For those with stroke listed as their underlying cause of death, pneumonia and heart disease were common comorbidities (718 and 559 subjects, respectively). For other circulatory

TABLE 1
Count of all Circulatory Disease Deaths and Count of Deaths with Comorbidities by Follow-Up Periods 1950–1976 and 1977–2003

	Follow-up period 1950–1976			Follow-up period 1977–2003		
		Count of deaths with at least one comorbidity			Count of deaths with at least one comorbidity	
Underlying cause of death	Count of deaths	N	Percentage	Count of deaths	N	Percentage
All circulatory disease	9,035	3,119	34.5%	10,017	4,150	41.4%
Heart disease	2,208	1,427	64.6%	2,633	1,947	73.9%
Rheumatic heart disease	173	142	82.1%	84	80	95.2%
Hypertensive heart disease	819	559	68.3%	514	478	93.0%
Ischemic heart disease	1,216	781	64.2%	2,035	1,437	70.6%
Stroke	5,322	2,793	52.5%	4,299	2,757	64.1%
Other circulatory disease	1,505	701	46.6%	3,085	1,428	46.3%
Heart failure	645	269	41.7%	2,185	906	41.5%

Notes. Comorbidities included here refer to all causes of death other than the underlying cause of death. Hierarchical classification of diseases was applied for circulatory diseases. For a case in which multiple diseases in the circulatory disease category, such as heart disease and stroke, occurred at the same time, one is considered an underlying cause of death and the other is labeled a comorbidity. Since these are both included in the all circulatory disease category, this case is counted in the category for underlying cause of death all circulatory disease with no comorbidities as well as in the category for the specific subtype underlying cause of death (e.g., heart disease) with one comorbidity. This classification system is used whenever both the underlying cause of death and the comorbidity are circulatory diseases.

disease, comorbid stroke was frequently listed (374 subjects); in more than half of these cases having comorbid stroke, the specific underlying cause of death was heart failure. The number of subjects with comorbid cancer was relatively small for any underlying cause of death.

Radiation-Related Risk for Combinations of Underlying Cause of Death and Comorbidities

To analyze the effects of radiation exposure on mortality from combinations of underlying cause of death and comorbidities, the ERR from radiation exposure was first estimated for mortality from underlying causes of death regardless of comorbidities (Table 3). Significant dose responses were observed for all circulatory disease, rheumatic heart disease, hypertensive heart disease, other circulatory disease and heart failure. The best model for each of these outcomes was a linear dose-response model. The ERRs at 1 Gy radiation ranged from 0.12 for all circulatory disease to 1.18 for rheumatic heart disease.

ERRs from radiation exposure were then estimated for mortality from combinations of underlying causes of death and comorbidities (Table 4). When cancer was comorbid with any of the underlying causes of death (all circulatory disease, heart disease, ischemic heart disease or stroke), the ERRs at 1 Gy radiation were significantly increased. ERRs ranged from 0.61 for all circulatory disease with comorbid cancer to 1.60 for ischemic heart disease with comorbid cancer. Among combinations of other comorbidities with the listed underlying causes of death, only heart disease as the underlying cause of death with comorbid diabetes had a significant dose response ($P = 0.010$). In the earlier period, comorbid pneumonia and diabetes mellitus tended to show relatively high ERRs compared to those same comorbidities in the later period, especially for comorbid diabetes with underlying cause as all circulatory disease ($P = 0.035$) and comorbid pneumonia with heart disease and ischemic heart disease ($P = 0.044$ and 0.029, respectively; Appendix Table A3).

In the 10,017 all circulatory disease deaths (ERR at 1 Gy = 0.117, $P = 0.002$), both the 5,867 deaths without comorbidities (ERR at 1 Gy = 0.103, $P = 0.033$) and the 4,150 deaths with at least one comorbidity (ERR at 1 Gy = 0.135, $P = 0.023$) had significantly increased risks of mortality. In addition, when the 177 subjects who had comorbid cancer were excluded from the 10,017 all circulatory disease deaths, the ERR from radiation exposure remained significant (N = 9,840, ERR at 1 Gy = 0.107, $P = 0.005$).

DISCUSSION

There are only a few published studies from Japan in which radiation-related risk of mortality has been evaluated while considering comorbidities. The distribution of comorbidities observed in this study was similar to that reported by Umeda *et al*. in 1988 (*6*). As for dose-response relationships for circulatory diseases as the underlying cause of death with and without comorbidities in the LSS, Shimizu *et al*. (*7*) showed significant ERRs for mortality from all circulatory disease, heart disease, stroke, hypertensive heart disease and heart failure deaths between 1950–2003, but not for ischemic heart disease. Since heart failure was excluded from the heart disease category in the current study and observation was limited to the recent period (1977–2003), the ERR was less than that in Shimizu's study and was not significant. When the 2,185 cases with heart failure as underlying cause of death were included in this category, a significant dose-response relationship for heart disease mortality was observed during the period of 1977–2003 (data not shown).

The focus of the current study was on comorbidities that have not been previously considered in radiation risk

TABLE 2
Number of Deaths with Combinations of Underlying Cause of Death and Comorbidities for Follow-Up Periods 1950–1976 and 1977–2003

Underlying cause of death	Comorbidity	1950–1976 N[a]	1977–2003 N	Underlying cause of death	Comorbidity	1950–1976 N[a]	1977–2003 N
All circulatory disease	Pneumonia	423	956	Stroke[c]	Heart disease[c]	1,005	559
	Renal disease	51	469		Rheumatic heart disease	3	5
	Diabetes mellitus	110	306		Hypertensive heart disease	944	476
	Cancer	56	177		Ischemic heart disease	68	111
	Other[b]	2,494	2,346		Pneumonia	282	718
Heart disease[c]	Stroke[c]	263	345		Renal disease	12	160
	Pneumonia	101	122		Diabetes mellitus	60	100
	Renal disease	22	137		Cancer	23	61
	Diabetes mellitus	44	128		Other	1,458	1,326
	Cancer	25	48	Other circulatory disease[c]	Heart disease	34	96
	Other	1,006	1,006		Rheumatic heart disease	0	2
Rheumatic heart disease[d]	Hypertensive heart disease[d]	7	0		Hypertensive heart disease	26	61
	Ischemic heart disease[d]	10	6		Ischemic heart disease	10	36
	Stroke	21	15		Stroke	74	374
	Pneumonia	6	4		Pneumonia	40	116
	Renal disease	1	3		Renal disease	17	172
	Diabetes mellitus	1	1		Diabetes mellitus	6	78
	Cancer	1	1		Cancer	8	68
	Other	102	53		Other	532	634
Hypertensive heart disease[d]	Rheumatic heart disease[d]	1	0	Heart failure[e]	Heart disease	0	35
	Ischemic heart disease	16	5		Rheumatic heart disease	0	0
	Stroke	102	74		Hypertensive heart disease	0	27
	Pneumonia	50	28		Ischemic heart disease	0	10
	Renal disease	11	64		Stroke	26	245
	Diabetes mellitus	18	22		Pneumonia	16	73
	Cancer	11	5		Renal disease	3	97
	Other	370	303		Diabetes mellitus	3	46
Ischemic heart disease[d]	Rheumatic heart disease	7	2		Cancer	5	47
	Hypertensive heart disease	91	205		Other	221	419
	Stroke	140	256				
	Pneumonia	45	90				
	Renal disease	10	70				
	Diabetes mellitus	25	105				
	Cancer	13	42				
	Other	480	802				

Note. When a case has all circulatory disease as the underlying cause of death and two or more comorbidities that were categorized in the ''Comorbidity'' column, the case is counted again for each comorbidity.

[a] Number of deaths.

[b] Includes illness or disease other than targeted.

[c] Subtype of all circulatory disease (see Appendix Table A1).

[d] Subtype of heart disease (see Appendix Table A1).

[e] Subtype of other circulatory disease (see Appendix Table A1).

estimates in the LSS. ERRs of radiation exposure for mortality from the underlying causes of death (all circulatory disease, heart disease, ischemic heart disease and stroke) were significant when cancer was comorbid. ERRs were not, however, observed for combinations of these underlying causes of death with other comorbidities, except where diabetes was comorbid with heart disease. The ERR at 1 Gy of mortality from all circulatory disease with comorbid cancer was approximately six times higher than the ERR of all circulatory disease as the underlying cause of death, regardless of comorbidities. Furthermore, heart disease, ischemic heart disease and stroke with comorbid cancer showed higher ERRs (i.e., compared to the results in shown in Table 3). The ERR of all circulatory disease with comorbid cancer was particularly high at doses of $\geq$1.0 Gy, so that the quadratic dose response had the best fit (Fig. 1 and Appendix Table A4). Because the number of cases at high-dose levels was small and the models for estimating ERR were different, we could not determine if the higher ERRs were anomalous, the result of the dissimilarity of

TABLE 3
Relationship Between Radiation Dose and Circulatory Disease Mortality with Underlying Cause of Death as All Circulatory Disease, for Follow-Up Period 1977–2003

Underlying cause of death	N[a]	Model class[b]	ERR at 1 Gy	95% CI[c]	*P* value[d]
All circulatory disease	10,017	L	0.117	(0.04, 0.20)	0.002
Heart disease	2,633	L	0.128	(–0.02, 0.30)	0.099
Rheumatic heart disease	84	L	1.175	(0.13, 2.93)	0.022
Hypertensive heart disease	514	L	0.475	(0.05, 1.04)	0.026
Ischemic heart disease	2,035	L	0.0001	(–0.14, 0.17)	>0.5
Stroke	4,299	L	0.086	(–0.02, 0.21)	0.124
Other circulatory disease	3,085	L	0.192	(0.05, 0.35)	0.007
Heart failure	2,185	L	0.287	(0.11, 0.49)	<0.001

[a] The number of deaths from underlying cause of death.
[b] L = based on a linear dose-response model, Q= based on a quadratic dose-response model (same as Table 4).
[c] Likelihood-based 95% confidence interval.
[d] Two-sided *P* value based on likelihood ratio method.
[e] 95% lower bound last estimate; no feasible lower bound could be estimated.

models or some radiological pathogenetic interaction between circulatory disease and cancer to increase fatality. The distribution of cancer sites is thought to generally reflect the pattern of cancer incidence observed in the LSS (*27*), but detailed interpretation regarding radiosensitivity and survivability of the site-specific distribution of comorbid cancers in this study is difficult because of the small numbers of cases (Appendix Table A5). When the 177 deaths with comorbid cancer were excluded from the analysis, the ERR of mortality from all circulatory disease was still elevated. This finding suggests that radiation exposure increases the risk of circulatory disease mortality independent of other possible risk factors.

A significant dose-response relationship for heart disease mortality was observed in cases with diabetes mellitus comorbidity. Mortality of all circulatory disease with comorbid diabetes also had a positive ERR over radiation exposure, although the value was not significant. As both diabetes (*13, 14*) and radiation exposure (*28, 29, 30*) are thought to accelerate vascular atherosclerosis, persons exposed to radiation may be more vulnerable to circulatory disease with comorbid diabetes. Although the underlying causes of death by other circulatory disease and heart failure (which comprised the majority of other circulatory disease cases) had high radiation-associated ERRs when comorbidities were disregarded, ERRs with comorbidities included were not significant. This lack of significance is probably related to the smaller number of cases per combination of underlying cause of death and comorbidity. Since heart failure is actually an umbrella category for a number of miscellaneous pathogenic conditions, even a naïve interpretation of these results is difficult.

Rules for issuing death certificates and coding underlying causes of death were determined using WHO guidelines. Cancer is generally considered the major cause of death. However, these rules were likely not correctly applied on every occasion, an oversight possibly due to societal pressure. In the past, cancer deaths were sometimes attributed to noncancer diseases due to social stigma attached to cancer. This societal trend may have influenced doctors issuing death certificates to list other diseases as the underlying causes of death, and selecting cancer as merely a comorbidity. Alternatively, the significance of cancer in a patient's death may have been underestimated by doctors in some circumstances.

From studies concerning misclassification by Ishida *et al.* (*4*), Yamamoto *et al.* (*31*), Sposto *et al.* (*32*), Jablon *et al.* (*33*) and Ron *et al.* (*20*), comparisons of certified causes of death and autopsy diagnoses have shown that the confirmation (or agreement) rates varied widely among causes of death. For example, Ron *et al.* reported that the confirmation rate between the major cause of death from autopsies between 1976–1987 and the underlying causes of death listed on death certificates within approximately the same time period was only 44% for a combined diagnosis, including heart disease and several other types of circulatory disease, and only 61% for stroke. In light of these findings, the results of current study may represent only spurious radiation effects on circulatory disease mortality due to misclassification.

However, not all circulatory disease deaths with comorbid cancer were necessarily misclassified. Only 10 years of overlap exist between the period during which autopsies were performed (1950–1987) and the period of interest to this study (1977–2003). The autopsies were performed for only 817 LSS cohort members in the period of 1976–1987, and these results were likely biased. In the explanation of this bias, Ron *et al.* states that the reason autopsies were generally performed was to identify the cause of death when the cause was previously uncertain (*20*). Moreover, cardiovascular diseases are often functional disorders without specific histological identifiers. They may not, therefore, be easy to confirm postmortem, and must often be indicated by antemortem data. Systemic information, such as the presence of hypertension or lifestyle risk factors, can be used for such diagnoses. Such information is sometimes found in a few notes in the comments section of the death certificate, although it may not be recorded at all. Shimizu *et al.* reported that high proportions of autopsy cases had stroke (86%) and/or heart disease (92%) listed as a major cause of death or as a comorbidity (*7, 34*). Finally, cancers

TABLE 4
Relationship Between Radiation Dose and Mortality from Combinations of Underlying Cause of Death and Comorbidities, 1977–2003

Underlying cause of death	Comorbidity	N[a]	Model class	ERR at 1 Gy	95% CI	*P* value
All circulatory disease	Pneumonia	956	L	0.041	(–0.18, 0.32)	>0.5
	Renal disease	469	L	–0.014	(–0.31, 0.37)[b]	>0.5
	Diabetes mellitus	306	L	0.439	(–0.02, 1.12)	0.065
	Cancer	177	Q	0.612	(0.13, 1.41)	0.005
Heart disease[c]	Stroke[c]	345	L	0.171	(–0.21, 0.72)	0.438
	Pneumonia	122	L	0.026	(–0.69, 1.21)[b]	>0.5
	Renal disease	137	L	0.149	(–0.40, 1.01)[b]	>0.5
	Diabetes mellitus	128	Q	0.616	(0.10, 1.46)	0.010
	Cancer	48	L	1.488	(0.09, 4.28)	0.030
Hypertensive heart disease[d]	Stroke	74	L	0.602	(–0.60, 2.58)[b]	0.363
	Renal disease	64	L	–0.045	(–0.93, 0.84)[f]	>0.5
Ischemic heart disease[d]	Hypertensive heart disease[c]	205	Q	0.035	(–0.23, 0.48)[b]	>0.5
	Stroke	256	L	0.111	(–0.32, 0.70)[b]	>0.5
	Pneumonia	90	L	–0.234[e]	(–0.93, 1.09)[b]	>0.5
	Renal disease	70	L	0.390	(–0.44, 1.87)[b]	0.396
	Diabetes mellitus	105	L	0.505	(–0.15, 1.63)[b]	0.166
	Cancer	42	L	1.602	(0.07, 4.86)	0.034
Stroke[c]	Heart disease[c]	559	L	–0.191	(–0.40, 0.09)[b]	0.161
	Hypertensive heart disease[d]	476	L	–0.208	(–0.41, 0.08)[b]	0.131
	Ischemic heart disease[d]	111	L	0.263	(–0.75, 1.80)[b]	>0.5
	Pneumonia	718	L	0.061	(–0.20, 0.40)	>0.5
	Renal disease	160	L	–0.181	(–0.52, 0.38)[b]	0.440
	Diabetes mellitus	100	L	–0.332[e]	(–0.96, 0.29)[f]	0.436
	Cancer	61	Q	1.544	(0.37, 3.91)	0.001
Other circulatory disease[c]	Heart disease	96	L	0.268	(–0.54, 1.60)[b]	>0.5
	Hypertensive heart disease	61	L	0.375	(–0.92, 2.42)[b]	>0.5
	Stroke	374	L	0.229	(–0.13, 0.74)	0.249
	Pneumonia	116	L	0.172	(–0.43, 1.14)[b]	>0.5
	Renal disease	172	L	0.073	(–0.54, 0.89)[b]	>0.5
	Diabetes mellitus	78	L	0.291	(–0.47, 1.66)[b]	>0.5
	Cancer	68	L	–0.593[g]	(–1.22, 0.04)[f]	0.287
Heart failure[h]	Stroke	245	Q	0.255	(–0.03, 0.74)	0.095
	Pneumonia	73	L	0.136	(–0.56, 1.49)[b]	>0.5
	Renal disease	97	L	0.893	(–0.08, 2.48)	0.079
	Diabetes mellitus	46	L	0.503	(–0.56, 2.78)[b]	0.428
	Cancer	47	L	–0.371[e]	(–1.45, 0.95)[f]	>0.5

Note. The number of cases for a combination of rheumatic heart disease as underlying cause of death and any comorbidity was not sufficient for analysis.

[a] The number of deaths from the combination of underlying cause of death and comorbidity.
[b] 95% lower bound last estimate; no feasible lower bound could be estimated.
[c] Subtype of all circulatory disease (see Appendix Table A1).
[d] Subtype of heart disease (see Appendix Table A1).
[e] ERR at 1 Gy and *P* value represent estimates made with person-year weighted mean dose restricted to less than 2 Gy radiation.
[f] Based on Wald's confidence interval; no feasible likelihood-based bound could be estimated.
[g] ERR at 1 Gy and *P* value represent estimates made with person-year weighted mean dose restricted to less than 1.5 Gy radiation.
[h] Subtype of other circulatory disease (see Appendix Table A1).

might be truly recorded as comorbidities if they had fully healed or were unmistakably nonfatal.

A limitation of this study was that information about causes of death was dependent upon death certificates. Coincident diseases could not be examined using medical charts. Yet, even if it had been possible, this type of analysis would not be realistic for such large numbers of deaths. Although rules for issuing death certificates and for describing and coding underlying and contributing causes of death were established by WHO, actual records on death certificates were not always in accordance with these rules. It is expected that standardization of records and accuracy in cause of death and comorbidities on death certificates will improve with advances in medicine and better compliance with death certificate guidelines. Another limitation of this study is the small number of cases for each underlying cause of death and comorbidity combination. The large number of possible combinations in addition to the small number of cases per combination indicates that this type of analysis has low statistical power. Since the current analyses were performed only for combinations with at least 40 cases, however, loss of power is believed to be limited.

In this study, three models that have been commonly used in LSS analyses were considered: the linear, quadratic and

linear-quadratic models (*1*). We report here on our initial, simple analysis of radiation dose response with a focus on comorbidities, and more detailed studies will be necessary in the future.

In conclusion, significantly elevated radiation risks of mortality from all circulatory diseases as the underlying cause of death reported on death certificates were observed among LSS cohort members. Furthermore, significant associations with radiation were observed for mortality from heart disease, stroke and ischemic heart disease as underlying causes of death with comorbid cancer and several other comorbidities. Further investigation is required to ascertain if the high ERRs with comorbid cancers were anomalous due to the small number of cases, based on some dissimilarity in statistical methodologies or if this might suggest some pathogenetic basis to increased fatality. It is our hope that this study provides useful information for atomic bomb survivors and other interested parties, as well as for future medical research.

APPENDIX

TABLE A1
Disease Categories Based on the International Classification of Disease (ICD), 7th–10th Editions

	ICD-10	ICD-9	ICD-8	ICD-7
All circulatory disease	G45, I00–I99, M30	390–459	390–458	330–334, 400–468
Heart disease	I00–I13, I15, I20–I25	390–398, 401–405, 410–414	390–398, 400–404, 410–414	400–416, 420, 440–447
Rheumatic heart disease	I00–I09	390–398	390–398	400–416
Hypertensive heart disease	I10–I13, I15	401–405	400.0, 400.1, 400.3, 400.9, 401–404	440–447
Ischemic heart disease	I20–I25	410–414	410–414	420
Stroke	I60–I69, G45	430–438	400.2, 430–438	330–334
Other circulatory disease	I26–I52, I70–I99, M30	415–429, 440–459	420–429, 440–458	421–434, 450–468
Heart failure	I50	428	427, 428	434
Pneumonia	J10–J18 (0, 1, 8, 9)	480–487	470–486	480–493
Renal disease	N00–N19	580–589	580–584	590–594
Diabetes mellitus	E10–E14	250	250	260
Cancer	C00–C97	140–208	140–209	140–205
All solid cancer	C00–C80	140–199	140–199	140–199
Esophagus	C15	150	150	150
Stomach	C16	151	151	151
Colon	C18	153	153	153
Rectum	C19–C20	154	154	154
Liver	C22.0–C22.4, C22.7, C22.9	150.0–150.2	155, 197.8	155.0, 155.8, 156
Gallbladder	C23, C24	156	156	155.1
Pancreas	C25	157	157	157
Other digestive system	C26, C48	158, 159	158, 159	158, 159
Lung	C33, C34	162	162	162.0, 162.1, 162.8, 163
Breast	C50	174, 175	174	170
Uterus	C53, C54, C55.9	179–180, 182	180, 182.0, 182.9	171, 172, 174
Ovary	C56, C57.0–C57.4	183	183	175
Prostate	C61	185	185	177
Bladder	C67	188	188	181
Kidney parenchyma, renal and other urinary diseases	C64–C66, C68	189	189	180, 181.7, 181.8
Other solid cancer	Others in C00–C80	Others in 140–199	Others in 140–199	Others in 140–199
Leukemia	C91.0–C91.3, C91.5, C91.7, C91.9, C92.0–C92.5, C92.7, C92.9, C93, C94.0–C94.3, C94.7, C95	204–208	204–207	204
Malignant lymphoma	C81–C85, C91.4, C96	200–202	200–202	200–202, 205
Multiple myeloma	C88.7, C88.9, C90	203	203	203

TABLE A2
Relationship between Radiation Dose and Circulatory Disease Mortality by Underlying Cause of Death, 1950–1976 and 1950–2003

	Follow-up period 1950–1976					Follow-up period 1950–2003				
Underlying cause of death	N[a]	Model class[b]	ERR at 1 Gy	95% CI[c]	*P* value[d]	N	Model class	ERR at 1 Gy	95% CI	*P* value
All circulatory disease	9,035	L	0.113	(0.03, 0.20)	0.007	10,017	L	0.117	(0.04, 0.20)	0.002
Heart disease	2,208	Q	0.114	(0.02, 0.24)	0.021	2,633	L	0.128	(–0.02, 0.30)	0.099
Rheumatic heart disease	173	L	0.666	(0.04, 1.64)	0.035	84	L	1.175	(0.13, 2.93)	0.022
Hypertensive heart disease	819	L	0.256	(–0.03, 0.61)	0.080	514	L	0.475	(0.05, 1.04)	0.026
Ischemic heart disease	1,216	L	0.047	(–0.14, 0.27)	>0.5	2,035	L	0.0001	(–0.14, 0.17)	>0.5
Stroke	5,322	Q	0.065	(0.005, 0.14)	0.034	4,299	L	0.09	(–0.02, 0.21)	0.124
Other circulatory disease	1,505	L	0.045	(–0.150, 0.29)	>0.5	3,085	L	0.192	(0.05, 0.35)	0.007
Heart failure	645	L	–0.074	(–0.34, 0.27)	>0.5	2,185	L	0.287	(0.11, 0.49)	<0.001

[a] The number of deaths from underlying cause of death.
[b] L = based on a linear dose-response model, Q= based on a quadratic dose-response model (same as shown in Table A3).
[c] Likelihood-based 95% confidence interval.
[d] Two-sided *P* value based on likelihood ratio method.
[e] 95% lower bound last estimate; no feasible lower bound could be estimated.

TABLE A3
Relationship between Radiation Dose and Mortality from Combinations of Underlying Cause of Death and Comorbidities, 1950–1976 and 1950–2003

Underlying cause of death	Comorbidity	N[a]	Model class	ERR at 1 Gy	95% CI	*P* value
		Follow-up period 1950–1976				
All circulatory disease	Pneumonia	423	L	0.335	(–0.04, 0.84)	0.084
	Renal disease	51	L	–0.063	(–0.96, 0.83)[b]	>0.5
	Diabetes mellitus	110	L	0.839	(0.04, 2.18)	0.035
	Cancer	56	L	–0.124	(–0.69, 1.64)[c]	>0.5
Heart disease[d]	Stroke[d]	263	L	0.085	(–0.34, 0.68)[c]	0.500
	Pneumonia	101	L	0.927	(0.02, 2.48)	0.044
	Diabetes mellitus	44	L	0.281	(–0.84, 2.28)[c]	>0.5
Hypertensive heart disease[e]	Stroke	102	L	0.467	(–0.39, 1.77)	0.296
	Pneumonia	50	L	–0.157	(–0.91, 0.60)[b]	>0.5
Ischemic heart disease[e]	Hypertensive HD[e]	91	LQ	–0.850[f]		
	Stroke	140	L	–0.025	(–0.53, 0.74)[c]	>0.5
	Pneumonia	45	L	1.850	(0.11, 5.45)	0.029
Stroke[d]	Heart disease[d]	1,005	L	0.030	(–0.16, 0.28)	>0.5
	Hypertensive HD	944	L	–0.010	(–0.20, 0.24)	>0.5
	Ischemic HD[e]	68	L	1.866	(0.18, 5.39)	0.022
	Pneumonia	282	L	0.045	(–0.34, 0.58)[c]	>0.5
	Diabetes mellitus	60	Q	0.850	(0.09, 2.48)	0.016
Other circulatory disease[d]	Stroke	74	L	–0.433[g]	(–1.17, 0.30)[b]	>0.5
	Pneumonia	40	L	1.323	(–0.39, 4.49)[c]	0.096
		Follow-up period 1950–2003				
All circulatory disease	Pneumonia	1,379	L	0.135	(–0.06, 0.37)	0.197
	Renal disease	520	L	–0.045	(–0.31, 0.31)[c]	>0.5
	Diabetes mellitus	416	Q	0.317	(0.07, 0.68)	0.008
	Cancer	233	L	0.733	(0.12, 1.66)	0.014
Heart disease)[d]	Stroke[d]	608	L	0.061	(–0.21, 0.43)	>0.5
	Pneumonia	223	L	0.555	(–0.06, 1.55)	0.088
	Renal disease	159	L	0.213	(–0.35, 1.03)[c]	0.485
	Diabetes mellitus	172	Q	0.501	(0.07, 1.18)	0.014
	Cancer	73	L	1.005	(–0.03, 2.88)	0.061
Hypertensive heart disease[e]	Stroke	176	L	0.523	(–0.17, 1.55)	0.162
	Pneumonia	78	L	0.389	(–0.59, 2.35)	>0.5
	Renal disease	75	L	–0.065	(–0.87, 0.74)	>0.5
	Diabetes mellitus	40	L	0.538	(–0.60, 2.70)	0.378
Ischemic heart disease[e]	Hypertensive HD[e]	296	L	–0.071	(–0.36, 0.38)[c]	>0.5
	Stroke	396	Q	0.064	(–0.15, 0.39)	>0.5
	Pneumonia	135	L	0.182	(–0.40, 1.13)[c]	>0.5
	Renal disease	80	L	0.504	(–0.35, 1.91)[c]	0.252

Continued on next page

TABLE A3
Continued.

Follow-up period 1950–1976						
Underlying cause of death	Comorbidity	N[a]	Model class	ERR at 1 Gy	95% CI	*P* value
	Diabetes mellitus	130	L	0.453	(–0.14, 1.42)	0.165
	Cancer	55	L	1.289	(0.01, 3.78)	0.047
Stroke[d]	Heart disease[d]	1564	L	–0.051	(–0.20, 0.13)	>0.5
	Hypertensive heart disease[e]	1,420	LQ	–0.222[i]		
	Ischemic heart disease[e]	179	L	0.872	(–0.005, 2.26)	0.052
	Pneumonia	1,000	L	0.056	(–0.16, 0.33)	>0.5
	Renal disease	172	L	–0.204	(–0.51, 0.32)[c]	0.361
	Diabetes mellitus	160	L	0.247	(–0.21, 1.04)	0.374
	Cancer	84	Q	1.193	(0.26, 2.96)	0.003
Other circulatory disease[d]	Heart disease	130	L	0.599	(–0.19, 1.85)	0.164
	Hypertensive heart disease	87	L	0.483	(–0.49, 2.05)[c]	0.359
	Ischemic heart disease	46	L	0.792	(–0.57, 3.38)	0.280
	Stroke	448	L	0.081	(–0.21, 0.49)	>0.5
	Pneumonia	156	L	0.418	(–0.17, 1.35)	0.200
	Renal disease	189	L	–0.077	(–0.59, 0.63)[c]	>0.5
	Diabetes mellitus	84	L	0.347	(–0.44, 1.70)[c]	0.429
	Cancer	76	L	–0.667[j]	(–1.11, –0.23)[c]	0.176
Heart failure[g]	Stroke	271	Q	0.207	(–0.09, 0.65)[c]	0.143
	Pneumonia	89	L	0.516	(–0.35, 1.92)[c]	0.241
	Renal disease	100	L	0.809	(–0.12, 2.32)	0.101
	Diabetes mellitus	49	L	0.351	(–0.55, 2.35)[c]	>0.5
	Cancer	52	L	–0.489[h]	(–1.11, 0.12)[c]	0.432

Note. The number of cases for a combination of rheumatic heart disease as the underlying cause of death and any comorbidity was not sufficient for analyses.

[a] The number of deaths having a combination between underlying causes of death and comorbidity.

[b] Based on Wald's confidence interval; no feasible likelihood-based bound could be estimated.

[c] 5% lower bound last estimate; no feasible lower bound could be estimated.

[d] Subtype of all circulatory disease (see Table A1).

[e] Subtype of heart disease (see Table A1).

[f] Based on a linear-quadratic dose-response model, parameter estimates are –1.44 ($P = 0.065$) for linear term and 0.59 ($P = 0.079$) for quadratic term.

[g] Subtype of other circulatory disease (see Table A1).

[h] ERR at 1 Gy and *P* value represent estimates made with person-year weighted mean dose restricted to less than 2 Gy radiation.

[i] Based on a linear-quadratic dose-response model, parameter estimates are –0.44 ($P = 0.033$) for linear term and 0.21 ($P = 0.054$) for quadratic term.

[j] ERR at 1 Gy and *P* value represent estimates made with person-year weighted mean dose restricted to <1.5 Gy radiation.

TABLE A4
ERR of All Circulatory Disease as an Underlying Cause of Death with Comorbid Cancer by Radiation Dose Category

Dose category[a]	N	ERR[b]	*P* value (Wald's test)
<0.005 Gy	82	-	-
0.005–0.02 Gy	31	0.262	0.411
0.02–0.04 Gy	14	0.255	>0.5
0.04–0.06 Gy	6	–0.233	>0.5
0.06–0.10 Gy	5	–0.414	0.285
0.10–0.2 Gy	7	–0.367	0.297
0.2–0.25 Gy	5	0.738	0.267
0.25–0.5 Gy	10	0.148	>0.5
0.5–1.0 Gy	6	0.072	>0.5
1.0–1.25 Gy	5	3.129	0.004
≥1.25 Gy	6	1.563	0.042

Note. See Fig. A1

[a] Weighted absorbed colon dose category.

[b] ERR per Gy.

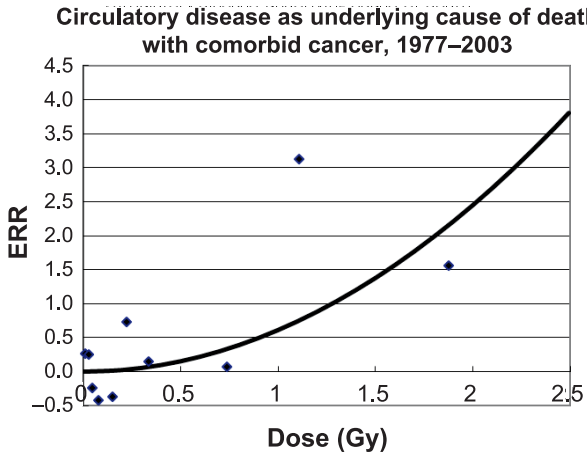

FIG. A1. ERR of all circulatory disease as an underlying cause of death with comorbid cancer by radiation dose category (as shown in Table A4).

TABLE A5
Number of Deaths with the Underlying Cause as all Circulatory Disease, with Comorbid Cancer by Site and Radiation Dose

	Radiation dose[a]			
Comorbid cancer site	<5 mGy	5 mGy–1Gy	>1 Gy	Total[b]
All cancers	82	84	11	177
All solid cancers	75	78	11	164
Cancers of specific sites				
Esophagus	2	1	1	4
Stomach	18	16	2	36
Colon	7	15	1	23
Rectum	0	4	1	5
Liver	2	1	0	3
Gallbladder	1	3	0	4
Pancreas	3	2	0	5
Other digestive systems	0	1	0	1
Lung	12	8	0	20
Breast	7	6	2	15
Uterus	1	3	0	4
Ovary	1	0	0	1
Prostate	5	1	1	7
Bladder	6	3	0	9
Kidney parenchyma, renal and other urinary	2	1	0	3
Other solid cancer	11	15	3	29
Lymphoid and hematopoietic malignancies				
Leukemia	3	2	1	6
Malignant lymphoma	4	3	0	7
Multiple myeloma	1	1	0	2

[a] Weighted absorbed colon dose.
[b] Total number of deaths, with all circulatory disease as the underlying cause, for each cormorbid cancer site. For two or more overlapping comorbid cancer sites, the case was counted for each site.

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ERRATA

Volume **187**, number 1, p. 20–31 (2017) in the article ''Mortality Analysis of the Life Span Study (LSS) Cohort Taking into Account Multiple Causes of Death Indicated in Death Certificates'' by Ayako Takamori, Ikuno Takahashi, Fumiyoshi Kasagi, Akihiko Suyama, Kotaro Ozasa and Takashi Yanagawa, the authors have identified several errors in their report.

1. Page 25, Table 3: Footnote ''^{e} 95% lower bound last estimate; no feasible lower bound could be estimated'' should be deleted.

2. Page 28, Table A2: The right panel (1950–2003) should be replaced with the following. Current contents indicate the results for period 1977–2003.

Follow-up period 1950-2003				
N	Model class	ERR at 1Gy	95%CI	*P* value
19052	L	0.101	(0.05 , 0.16)	< 0.001
4841	Q	0.080	(0.01 , 0.16)	0.014
257	L	0.843	(0.25 , 1.66)	0.002
1333	Q	0.164	(0.01 , 0.36)	0.029
3251	L	0.021	(-0.09 , 0.15)	> 0.5
9621	Q	0.060	(0.01 , 0.11)	0.008
4590	L	0.119	(0.01 , 0.24)	0.037
2830	L	0.203	(0.05 , 0.37)	0.007

3. Page 29, **Table A3**: In footnote ''*c*'', ''5%'' should be ''95%''.