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Comparison of All Solid Cancer Mortality and Incidence Dose-Response in the Life Span Study of Atomic Bomb Survivors, 1958–2009

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Recent analysis of all solid cancer incidence (1958–2009) in the Life Span Study (LSS) revealed evidence of upward curvature in the radiation dose response among males but not females. Upward curvature in sex-averaged excess relative risk (ERR) for all solid cancer mortality (1950–2003) was also observed in the 0–2 Gy dose range. As reasons for non-linearity in the LSS are not completely understood, we conducted dose-response analyses for all solid cancer mortality and incidence applying similar methods [1958–2009 follow-up, DS02R1 doses, including subjects not-in-city (NIC) at the time of the bombing] and statistical models. Incident cancers were ascertained from Hiroshima and Nagasaki cancer registries, while cause of death was ascertained from death certificates throughout Japan. The study included 105,444 LSS subjects who were alive and not known to have cancer before January 1, 1958 (80,205 with dose estimates and 25,239 NIC subjects). Between 1958 and 2009, there were 3.1 million person-years (PY) and 22,538 solid cancers for incidence analysis and 3.8 million PY and 15,419 solid cancer deaths for mortality analysis. We fitted sex-specific ERR models adjusted for smoking to both types of data. Over the entire range of doses, solid cancer mortality dose-response exhibited a borderline significant upward curvature among males ($P = 0.062$) and significant upward curvature among females ($P = 0.010$); for solid cancer incidence, as before, we found a significant upward curvature among males ($P = 0.001$) but not among females ($P = 0.624$). The sex difference in magnitude of dose-response curvature was statistically significant for cancer incidence ($P = 0.017$) but not for cancer mortality ($P = 0.781$). The results of analyses in the 0–2 Gy range and restricted lower dose ranges generally supported inferences made about the sex-specific dose-response shape over the entire range of doses for each outcome. Patterns of sex-specific curvature by calendar period (1958–1987 vs. 1988–2009) and age at exposure (0–19 vs. 20–83) varied between mortality and incidence data, particularly among females, although for each outcome there was an indication of curvature among 0–19-year-old male survivors in both calendar periods and among 0–19-year-old female survivors in the recent period. Collectively, our findings indicate that the upward curvature in all solid cancer dose response in the LSS is neither specific to males nor to incidence data; its evidence appears to depend on the composition of sites comprising all solid cancer group and age at exposure or time. Further follow up and site-specific analyses of cancer mortality and incidence will be important to confirm the emerging trend in dose-response curvature among young survivors and unveil the contributing factors and sites. **© 2022 by Radiation Research Society**

The Life Span Study (LSS) of Japanese atomic bomb survivors has provided valuable information on the health effects of ionizing radiation and quantitative estimates of radiation risk for scientific and radiation protection purposes (*1*). The study is notable for its size, population exposed at all ages to a wide range of well-characterized doses, and long-term follow-up spanning over five decades (*2*). Information used for cancer risk assessment is derived from a nationwide monitoring of death-certificate based mortality data since 1950 (*2, 3*) and cancer incidence data available from regional cancer registries in Hiroshima and Nagasaki since 1958 (*4*). Despite differences in accuracy, completeness, and calendar year availability of cancer data from the two follow-up methods, radiation risk estimates and risk patterns for all solid cancer in the LSS have been largely similar (*3, 5–8*). Until recently, the radiation-associated risk for all solid cancers as a group was well described by a linear dose response, in which excess relative risk (ERR) decreased independently with increasing attained age and age at exposure, with the ERR estimates for mortality and incidence ranging between 0.27 to 0.36 per Gy (at age 70 after exposure at age 30) for males and between 0.58 to 0.66 per Gy for females (*3, 6, 8*). However, the most recent all

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solid cancer incidence report for the 1958–2009 period found significant upward curvature in the dose response for males over the full range of doses as well as over restricted dose ranges and no evidence against linearity for females (*7*). The last mortality report for the 1950–2003 period also observed a significant upward curvature in sex-averaged ERR for all solid cancer in the dose range 0–2 Gy (*3*), which was attributed to curvature among males (*9*). An important implication of the upward curvature in dose response, if real, is that the radiation risks for all solid cancer derived from a linear-dose-response model would overestimate the risks at low doses and underestimate the risks at high doses of radiation.

In the incidence report, we evaluated several factors as possible sources of upward curvature in the dose response for all solid cancer (*7*). We found that the apparent curvature among males could not be fully explained by revision of doses (*9*), adjustment for smoking, exclusion of autopsy-only cases, high-dose survivors or subjects not in city (NIC) at the time of the bombings, although revised dose estimates had relatively more impact on curvature than other changes. In a follow-up study of cancer incidence (*10*), Cologne et al. found that, by excluding individual cancer sites from all solid cancers as a group, there was large variation in the magnitude of the estimated dose-response curvature for the remaining sites for both males and females. The study also offered an example of how misspecification of the background rates for individual cancer sites in a single model applied to the combined outcome could influence an inference about the dose-response shape.

The upward curvature in dose response for all solid cancer mortality has been less well investigated than that for cancer incidence. Ozasa et al. found that evidence for sex-averaged curvature in ERR below 2 Gy [DS02 (*11*)] became stronger as the mortality follow-up increased (*3*), but whether this trend continued with additional follow-up is unclear. When updated dose estimates (DS02R1) were applied to mortality data through 2003, evidence for male curvature in all solid cancer dose response below 2 Gy decreased while evidence for female curvature increased (*9*). Recently, Little at al. used several methods to adjust for errors in dose estimates (DS02R1) while re-analyzing the Ozasa et al. data and found significant upward dose-response curvature for both sexes below 3 Gy (*12*). The risk models applied to all solid cancer mortality data by Little et al. were different from both Ozasa at al. (*3*) and Grant et al. (*7*). To what extent inconsistent findings regarding sex-specific dose-response curvature in mortality and incidence data are related to different follow-up period or applied statistical models (e.g., stratified background vs. parametric background, NIC subjects excluded vs. included, unadjusted for smoking vs. smoking adjusted, respectively) remains to be determined.

The objective of our study was twofold: (1) characterize the shape of sex-specific all solid cancer mortality dose response extending follow up in the previous report (*3*) by six years and (2) gain additional insights into potential sources of curvature by comparing the dose response for all solid cancer mortality and incidence data derived from similar statistical models. To this end, we used mortality follow-up through 2009, included NIC subjects, and applied the same doses (DS02R1) and models as in the analysis of all solid cancer incidence data (*7*). We performed sensitivity analyses of updated cancer mortality data (i.e., using data for the 1950–2003 and 1950–2009, without NIC, and under different statistical models) to facilitate comparison with previous mortality reports.

MATERIALS AND METHODS

Study Population and Case Ascertainment

Study methods have been described previously in detail (*3, 7*). In brief, the LSS consists of 120,321 subjects including 93,741 atomic bomb survivors from Hiroshima and Nagasaki and 26,850 subjects who were resident, but not in either city at the time of the bombings. All cohort members have been followed since October 1, 1950 for their vital status and cause of death using a nationwide family registry system (*koseki*) and death certification, which provides virtually complete coverage for all of Japan (*2, 3*). Ascertainment of incident cancer cases has been conducted since 1958 via linkage of LSS data with regional cancer registries in Hiroshima and Nagasaki (*4*). The end of follow-up for both cancer mortality and incidence in this study was December 31, 2009.

Causes of death were classified by Radiation Effects Research Foundation (RERF) staff trained in nosology using the relevant version of the International Classification of Diseases (ICD) 7th–10th editions. In the mortality analysis, as in other mortality reports (*3*), cases were restricted to deaths with solid cancer listed as the underlying cause of death on the death certificate: ICD-7, ICD-8 and ICD-9 codes 140-199 and ICD-10 codes C00-C80. In the incidence analysis, all first primary incident cancers were coded according to the International Classification of Diseases for Oncology (ICD-O). Included in the solid cancer incidence category were first primary cancer cases defined as in Grant et al. (*7*), i.e., ICD-O-3 topography codes C00-C89 with behavior code 3 (malignant) plus brain and central nervous system tumors (CNS) with behavior code 0 (benign) or 1 (uncertain behavior). Lympho-hematopoietic malignancies (ICD-O-3 morphology codes 9590-9970) and otherwise eligible solid cancers diagnosed solely at autopsy (''autopsy only'') and not suspected clinically were not counted as cases and were censored at the time of diagnosis and death, respectively (*7*). The underlying cause of death for ''autopsy only'' cases was not changed after the autopsy.

Radiation Doses

Dosimetry System 2002 Revision 1 (DS02R1) was used to estimate individual organ doses received by those exposed to radiation from the bombings (*9*). The primary changes under this system were improved input parameters, i.e., survivor location and terrain shielding data (*9*). As noted before (*11*), dose estimates for individuals with total unweighted sum of neutron plus gamma-ray shielded kerma more than 4 Gy were truncated to 4 Gy. This was done to account for implausibly large estimates as survival at these exposure levels seems unlikely, especially given the post-bombing medical conditions in the two cities. However, the method for apportioning the levels of truncation between neutron and gamma doses was changed from before (*11*) to be proportional to the average neutron-to-gamma kerma ratio of survivors with estimated total shielded kerma of 4 Gy (*9*). As in previous analyses of all solid cancer data by Grant et al. (*7*) and Ozasa et al. (*3*), we used weighted absorbed colon doses calculated as the

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sum of gamma-ray dose plus ten times the neutron dose allowing for greater biological effectiveness of neutrons (*3*). The weighted absorbed colon doses were also corrected for dose error assuming 35% coefficient of variation (*13*).

Smoking Data

Self-reported information on smoking history was collected in mail surveys conducted among the LSS subjects in 1969, 1978 and 1991, and Adult Health Study (AHS) clinic-based questionnaires administered in 1963, 1965 and 1968 (*2*). AHS is a 20% subset of the LSS cohort whose members have been invited to undergo biennial clinical examination since 1958 (*14*). Overall, 60% of LSS members provided smoking information on at least one questionnaire (*7*). As in previous studies (*7, 15, 16*), smoking data were summarized with indicators of last known smoking status (never, past, current, and unknown) and, for smokers, age at starting, average intensity, and last age at which they were known to have smoked.

Data Organization

The analyses were based on a table of events (first primary solid cancer cases and solid cancer deaths) and person-time highly stratified by sex, city, age at exposure, attained age, time period, ground distance from the hypocenter (including a separate category for NIC), DS02R1 weighted absorbed colon dose, and a ''high-dose'' indicator (total shielded kerma >4 Gy). Further time-dependent stratification was made for smoking. All persons started with an ''unknown'' status of smoking. At the time smoking status became known, their cumulative pack-years and duration of smoking were calculated and allowed to increase until the end of follow-up or until they reported they had quit smoking. Smoking duration was calculated as the difference between attained age and age started smoking, while time since quitting was calculated as the difference between attained age and age at quitting. Cumulative pack-years were defined as the product of packs smoked per day (20 cigarettes per pack) and years smoked. Individuals without smoking data retained ''unknown'' status through the end of follow-up. To allow for both mortality and incidence cases in the same file, we treated cancer incidence as a time-dependent variable and additionally stratified a person-year table on time after the first cancer diagnosis. Incident cancer cases were counted at the time of diagnosis. With cancer mortality data, time of death was considered as date of the cancer onset. The primary outcomes were all solid cancer mortality and all solid cancer incidence.

For analysis of solid cancer mortality data, person-years (PY) of observation were computed from October 1, 1950 until the earliest: date of death, 110th birthday, or December 31, 2009 but for our primary analyses we used follow-up from 1958 to 2009 to be comparable to the analysis of cancer incidence data (see below). Also, for the main analysis of cancer mortality data, we utilized cancer deaths ascertained across all of Japan and, therefore, did not adjust PY for probability of migration. For analysis of cancer incidence, PY were computed from January 1, 1958 until the earliest: date of diagnosis of any cancer, date of death, 110th birthday, or December 31, 2009. As incident cancers among AHS and non-AHS LSS members were ascertained among residents of Hiroshima and Nagasaki prefectures, PY were adjusted for migration into and out of the cancer registries' catchment areas using city-, sex-, age- and calendar time-dependent residence probabilities estimated from the historical AHS contact data using logistic regression, as in (*7, 17*). During biennial visits to the RERF clinic, AHS members' address and contact information are routinely updated. The current migration estimates were derived from the AHS contact data updated through 2005 and applied to the full LSS cohort. For the 2005–2009 period, we assumed that migration probabilities were the same as for the 2001–2004 period.

Statistical Analyses

We used Poisson regression method to model all solid cancer mortality and incidence rates as functions of sex (*s*), city ©, attained age (*a*), year of birth (*b*), radiation dose (*d*), and smoking (*smk*). Radiation and smoking effects were described using a multiplicative joint effects model that could be summarized as:

$$\lambda_0\,(s,\,c,\,a,\,b,\,nic) \times [1 + ERR_{\mathrm{rad}}] \times [1 + ERR_{\mathrm{smk}}],$$

where λ_0 is the background rate for unexposed (0 dose) non-smokers, ERR_{rad} is the radiation excess relative risk and ERR_{smk} is smoking excess relative risk that describes changes in rates due to radiation and smoking relative to the background rates, respectively. Detailed model parametrization is shown in the Supplementary Materials (https://doi.org/10.1667/RADE-21-00059.1.S1). In modeling background rates, we distinguished between in-city and NIC subjects (*nic*) in such a way that radiation effects were quantified relative to in-city cohort members with 0 dose, including both minimally exposed proximal (<3,000 m) and distal (≥3,000 m) survivors (*18*). The effect of NIC was allowed to vary by city. In some models, we additionally allowed the background rates to vary between proximal and distal survivors within each city (see the Supplementary Materials; https://doi.org/10.1667/RADE-21-00059.1.S1) quantifying radiation effects relative to proximal survivors (*19*). The logarithms of background cancer rates were modeled as sex-specific quadratic splines in log attained age with a knot at 70 years and sex-specific linear trends in birth year.

Models of the form $\rho(d)\varepsilon(s,\,a,\,e,\,h)$ were used to characterize the ERR_{rad}. In these models, $\rho(d)$ describes shape of the dose response, while $\varepsilon(s,\,a,\,e,\,h)$ describes radiation effect modification by sex (*s*), attained age (*a*), age at exposure (*e*), and high dose (*h*), i.e., total shielded kerma >4 Gy. We considered several models to describe the sex-specific dose-response shape $\rho(d)$ including:

$$\beta_s d \quad \text{linear;}$$

$$\beta_{1s} d + \beta_{2s} d^2 \quad \text{linear quadratic; and}$$

$$\sum_i \theta_{is} I(D_i \le d \le D_{i+1}) \quad \text{categorical.}$$

where the ''s'' subscript indicates ''sex-specific.''

To assess dose-response parameters in the restricted dose range, we applied a disjoint dose-response model with two dose-response segments, below and above the dose cutpoint or D_{lim}. This method was employed for the analysis of LSS data previously (*7, 20*). Dose variables were defined as $d_{lo} = dI(d \le D_{lim})$ and $d_{hi} = dI(d > D_{lim})$ and the dose response was modeled as $\beta_{1s} d_{lo} + \beta_{2s} d_{lo}^2 + \text{gamma 1s} - \gamma_{1s1s} \mathrm{d_{hi}} + \text{gamma 2s} - \gamma_{2s2s} \mathrm{d_{hi}^2}$. Several dose cutpoints were considered (0.1, 0.25, 0.5, 1.0 and 2.0 Gy), all corresponding to the person-year tabulation cutpoints. The primary test for non-linearity involved testing the hypothesis that $\beta_{2s} = 0$ in the linear-quadratic model either on the full dose range or on the restricted dose ranges ($0 \le d \le D_{lim}$). To characterize the dose-response shape, we present a combination of linear (β_{1s}) and quadratic (β_{2s}) parameter estimates or linear (β_{1s}) and curvature (σ_s) parameter estimates, where $\sigma_s = \beta_{2s}/\beta_{1s}$, if $\beta_{1s} \ne 0$. Details concerning curvature parameter estimation and computation of 95% confidence intervals were described previously (*10*). Briefly, in the instances where linear coefficient in the linear-quadratic model is significantly different from zero, the confidence region consists of one interval. In the instances where the linear parameter is not significantly different from zero and the quadratic parameter is significantly different from zero, the confidence region consists of two separate intervals excluding zero. In the instances where both linear and quadratic dose parameters are not significantly different from zero, the confidence region for curvature is not informative and indicated as undefined. In all analyses in the restricted dose ranges,

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we used data for the entire LSS cohort and modeled background rates, radiation effect modification, and smoking effects in the same way as over the entire range of doses (see below). Dose-response plots present categorical dose response estimates, the fitted dose response, and a smoothed nonparametric dose response with confidence bounds. The smoothed dose-response and bounds were obtained using a weighted running-average smoother as described in (*7*).

Radiation effect modification was assessed using multiplicative log-linear models in which the modifying variables were scaled and centered so sex-specific dose-response parameters correspond to the risk at attained age 70 after exposure at age 30 and effect-modification parameters describe the change in ERR at 1 Gy for a given change in the factor of interest (such as powers of attained age and percent change per decade increase in age at exposure). As in Grant et al. (*7*), we allowed the effect of attained age on ERR to vary by sex, but fitted common age at exposure trend for males and females. To minimize influence of individuals with total shielded kerma >4 Gy on estimation of dose-response parameters, while allowing them to contribute information to estimation of the effect modification, the preferred ERR model included modification by ''high dose'' indicator. Similar allowance was made in all recent analyses of the LSS cancer mortality and incidence data (*7, 9*). In some analyses, we evaluated alternative ways of adjusting for ''high dose'' effect (see details in Supplementary Materials; https://doi.org/10.1667/RADE-21-00059.1.S1).

The ERR_{smk} was modeled as linear in time-dependent pack-years with allowance for additional log-linear dependence on log of smoking intensity (i.e., cigarettes smoked per day) and on log of time-dependent smoking duration (*7, 16*).

To investigate the impact of follow-up time on dose-response curvature, we used the approach of Cologne et al. (*20*) and dichotomized calendar time into 1958–1987 and 1988–2009 as this split total number of all solid cancers in mortality and incidence data approximately by half. Similarly, we explored heterogeneity in sex-specific curvature by age at the time of the bombing grouping survivors into two age groups: 0–19 years and 20 years or more. We fit eight dose-response parameters (separate linear and quadratic dose coefficients for each sex and calendar period or age at exposure: $2 \times 2 \times 2$) under common (for the entire follow-up or all ages at exposure) background and smoking parameters. To improve stability of dose-response estimates, effect modification was modelled over the entire follow-up period. In exploratory analyses, we also fit richer models with 16 dose-response parameters (allowing for simultaneous cross-classification of sex-specific dose coefficients by calendar period and age at exposure) and otherwise similar parametrization.

To evaluate whether the dose-response curvature in a single model applied to the combined mortality outcome (e.g., all solid cancer) could be related to unaccounted heterogeneity in background rates (or smoking effects) for individual cancer sites, as suggested by Cologne et al. (*10*), we used a joint endpoint analysis, analogous to the analysis of competing risks (*21*). For this analysis, we selected the four most common cancers (stomach, colon, liver, lung) and constructed a single dataset by stacking four PY tables (prepared as described under *Data Organization*) with each table having a set identifier variable and own case count variable. Using the stacked dataset, we fitted common dose-response parameters for combined mortality from the four cancers allowing for separate intercepts (to account for the multiplicity in PY), background, or smoking parameters for each cancer site. We also evaluated four site-specific dose-response models. Both site-specific and combined cancer mortality analyses for these sites were conducted in relation to weighted colon dose.

In supplementary analyses of cancer mortality data over the full range of doses and in the restricted dose ranges, we used follow-up for 1950–2003 and 1950–2009 periods, did not include NIC, and applied the same statistical model as in Report 14 by Ozasa et al. (*3*). In this model, sex-specific linear ERRs were estimated under stratified background (by sex, city, age at exposure, attained age, and distance to hypocenter) and effect modification by common to males and females attained age and age at exposure (see details in the Supplementary Materials; https://doi.org/10.1667/RADE-21-00059.1.S1). The model did not include adjustment for smoking or ''high dose'', although total shielded kerma doses >4 Gy were truncated. The only difference with the Report 14 analysis was use of the DS02R1 rather than DS02 dose estimates (*3*). We then modified the Report 14 model progressively towards the all solid cancer incidence model (*7*) and evaluated the change in dose-response parameters and quality of model fit. We also repeated analyses of cancer mortality, limiting deaths to those that occurred in Hiroshima and Nagasaki prefectures, while adjusting PY for probability of migration as in analyses of cancer incidence. Because place of residence at death was not available electronically for most NIC subjects, comparative analysis of solid cancer mortality and incidence data for this purpose had to be restricted to proximal and distal survivors (i.e., excluding NIC).

Estimated parameters, likelihood-based 95% confidence intervals (CI) (or, when indicated, Wald-based 95% CI), and likelihood-based ratio tests (LRT) were computed with the AMFIT module of the Epicure software (*22*). Relative quality of model fit was evaluated using Akaike information criterion (AIC). All tests were two-sided and considered statistically significant at α level of 0.05.

Ethical Considerations

This study was approved by the RERF Institutional Review Board via approval of Research Protocols 1-75 (Study of Life-span of A-bomb survivors, Hiroshima and Nagasaki) and 18-61 (Tumor registry study in Hiroshima and Nagasaki). The Hiroshima and Nagasaki prefectures approved the linkages between LSS cohort and data from the Cancer Registries, while Hiroshima and Nagasaki Medical Associations approved the linkages with their tumor tissue registries.

RESULTS

The total and dose category-specific number of people, PY, all solid cancer deaths and incident cases available for analyses of cancer mortality and incidence, are summarized in Table 1. Between 1950 and 2009, we ascertained 16,690 deaths from solid cancer among 113,186 LSS people with nearly 4.6 million PY. In the main analyses, mortality follow-up was restricted to the same calendar period as cancer incidence, i.e., 1958–2009. This reduced the total number of cancer deaths, people, and PY by 8%, 7%, and 17%, respectively; the magnitude of reduction was comparable among males and females. Consequently, analyses of cancer mortality data were based on 7,524 solid cancer deaths and 1.5 million PY among males and 7,895 solid cancer deaths and 2.3 million PY among females. By comparison, analyses of cancer incidence data were based on 10,473 solid cancer cases and 1.1 million PY among males (i.e., 39% more cases and 22% fewer PY) and 12,065 solid cancer cases and 1.9 million PY among females (i.e., 53% more cases and 18% fewer PY). Approximately 75% of all solid cancers and 79% of PY for in-city exposed males and females were accrued from those exposed to doses less than 0.1 Gy (in both cancer mortality and incidence data).

Composition of All Solid Cancers in Mortality and Incidence Data

The distribution of cancers by organ site in all solid cancer mortality and incidence data is shown separately for

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TABLE 1
Number of People, Person-Years of Observation, Solid Cancer Deaths, and Incident Cancer Cases in the LSS Cohort with Known Doses

Weighted colon dose (DS02R1), Gy	Mortality						Incidence		
	All Japan						Hiroshima/Nagasaki		
	1950–2009			1958–2009			1958–2009		
	People	PY	Deaths[a]	People[b]	PY	Deaths[a]	People[b]	PY[c]	Cases[d]
Both sexes									
NIC	26,528	1,082,559	3,921	25,239	928,404	3,705	25,239	760,159	5,222
Distal	25,176	1,009,190	3,586	23,165	833,095	3,290	23,165	666,335	4,851
<5	13,818	566,131	1,950	12,813	468,946	1,793	12,813	364,173	2,519
–0.1	29,658	1,203,042	4,207	27,511	994,564	3,829	27,511	806,303	5,674
–0.25	7,649	305,441	1,127	7,091	251,466	1,032	7,091	205,966	1,548
–0.5	4,744	188,785	767	4,429	155,217	714	4,429	126,699	1,083
–1	3,383	136,174	604	3,136	112,233	554	3,136	88,826	889
–2	1,682	66,447	393	1,565	54,451	373	1,565	42,209	560
2+ and K $\leq$ 4	266	10,641	74	244	8,723	70	244	6,604	100
2+ and K $>$ 4[e]	282	10,034	61	251	8,104	59	251	6,259	92
Total	**113,186**	**4,578,443**	**16,690**	**105,444**	**3,815,203**	**15,419**	**105,444**	**3,073,532**	**22,538**
Males									
NIC	11,145	428,969	2,005	10,488	361,766	1,898	10,488	287,532	2,560
Distal	10,699	400,276	1,792	9,639	326,276	1,650	9,639	251,092	2,359
<0.005	5,435	211,979	925	4,935	174,219	844	4,935	127,189	1,093
–0.1	12,249	471,927	2,029	11,175	386,590	1,848	11,175	301,768	2,635
–0.25	3,022	113,202	487	2,736	92,157	445	2,736	73,094	635
–0.5	1,840	69,122	350	1,697	56,241	331	1,697	44,481	461
–1	1,412	51,210	285	1,282	41,437	263	1,282	32,138	382
–2	778	28,655	189	716	23,173	179	716	17,804	254
2+ and K $\leq$ 4	130	4,736	34	115	3,833	33	115	2,887	44
2+ and K $>$ 4[e]	144	4,785	34	127	3,811	33	127	2,860	50
Total	**46,854**	**1,784,861**	**8,130**	**42,910**	**1,469,502**	**7,524**	**42,910**	**1,140,844**	**10,473**
Females									
NIC	15,383	653,590	1,916	14,751	566,638	1,807	14,751	472,627	2,662
Distal	14,477	608,914	1,794	13,526	506,819	1,640	13,526	415,244	2,492
<0.005	8,383	354,152	1,025	7,878	294,727	949	7,878	236,985	1,426
–0.1	17,409	731,115	2,178	16,336	607,974	1,981	16,336	504,535	3,039
–0.25	4,627	192,239	640	4,355	159,310	587	4,355	132,872	913
–0.5	2,904	119,663	417	2,732	98,976	383	2,732	82,217	622
–1	1,971	84,964	319	1,854	70,795	291	1,854	56,688	507
–2	904	37,791	204	849	31,279	194	849	24,405	306
2+ and K $\leq$ 4	136	5,904	40	129	4,890	37	129	3,717	56
2+ and K $>$ 4[e]	138	5,248	27	124	4,293	26	124	3,399	42
Total	**66,332**	**2,793,582**	**8,560**	**62,534**	**2,345,701**	**7,895**	**62,534**	**1,932,688**	**12,065**

Notes. LSS, Life Span Study. PY, person-years. NIC, individuals not in city at the time of the bombing. Distal, in-city survivors located $\geq$3,000 m from the hypocenter. K, total shielded kerma.

[a] Solid cancer deaths.

[b] 7,458 subjects who died before January 1, 1958 and 284 subjects known to have cancer prior to January 1, 1958 were excluded.

[c] PY adjusted for probability of migration.

[d] Incident solid cancers excluding ''autopsy only'' cases.

[e] Individuals with total shielded kerma >4 Gy.

males (Fig. 1A) and females (Fig. 1B). The proportion of liver cancer, pancreatic cancer, other digestive cancer, and lung cancer of all solid cancers combined was higher in the mortality data than incidence data for both males and females, while the proportion of colon cancer, rectal cancer, brain/CNS tumors, and thyroid cancer was higher in incidence than mortality data. Stomach cancer was the most common solid cancer in both types of data and sexes, although its proportion was somewhat higher in incidence data among males and in mortality data among females. For both sexes, the proportion of sex-specific cancers (i.e., prostate cancer in males and breast and genital cancers in females), which are generally less fatal, was higher in incidence than mortality data. Also, sex-specific cancers collectively accounted for a markedly higher fraction of all solid cancer cases among females than males, in both mortality (16% vs. 3%) and incidence data (26% vs. 8%).

Dose-Response Analyses over the Full Range of Doses

We first applied a linear ERR model with parametric background, multiplicative adjustment for smoking, and

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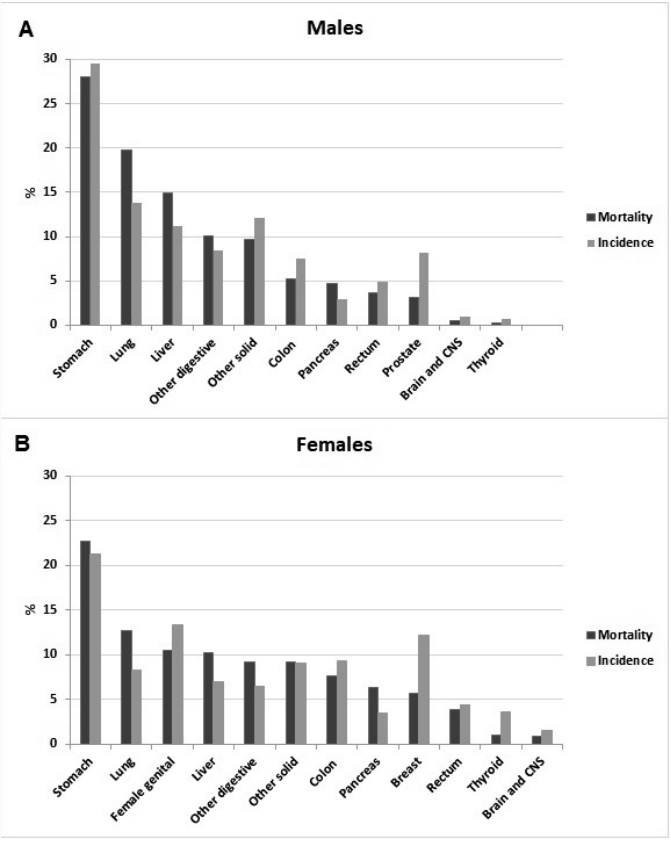


FIG. 1. Sex-specific distribution of all solid cancers according to anatomical site in the mortality and incidence LSS data. The bar height indicates percentage for a given site of all solid cancers combined in mortality data (dark bars) or incidence data (light bars); for each series, the percentages sum to 100%. Both mortality and incidence data are for 1958–2009 period; mortality cases are for entire Japan while incidence cases exclude cases diagnosed outside of Hiroshima and Nagasaki prefectures and ''autopsy only'' cases. *Note*. Other digestive cancers include oral, esophageal, gallbladder, other biliary cancers (other than liver, intrahepatic biliary, or gallbladder) and digestive cancers not categorized elsewhere. CNS, central nervous system. Other solid cancers include remaining solid cancers not categorized elsewhere.

effect modification (by sex, sex-specific attained age, age at exposure, and high dose) as in Grant et al. (*7*) to all solid cancer mortality and incidence data for the 1958–2009 period. The estimated sex-specific ERR per Gy and effect modification parameters for all solid cancer mortality and incidence were remarkably similar (Table 2). We then evaluated departure from linearity by adding a quadratic term in dose to the linear model for each sex (Table 3). As reported in Grant et al. (*7*), there was a significant upward curvature in dose response for all solid cancer incidence among males ($P = 0.001$) but not among females ($P = 0.624$). The all solid cancer mortality dose response exhibited a borderline significant upward curvature among males ($P = 0.062$) with estimated curvature slightly lower than that for cancer incidence. In contrast to solid cancer incidence, the solid cancer mortality dose response exhibited a statistically significant upward curvature among females ($P = 0.010$). The sex difference in magnitude of dose-response curvature was statistically significant for cancer incidence ($P = 0.017$) but not for cancer mortality ($P = 0.781$). The categorical point estimates and fitted sex-specific all solid cancer dose-response functions over the full range of doses are shown in Fig. 2A for female cancer mortality and Fig. 2C for male cancer mortality, Fig. 2B for female cancer incidence and Fig. 2D for male cancer incidence.

The solid cancer mortality results for the entire follow-up period (1950–2009) under the current model were similar to those for the 1958–2009 period: significant upward dose-response curvature was evident among both males and females (Supplementary Table S1; https://doi.org/10.1667/RADE-21-00059.1.S1). Also, sex-specific dose-response patterns for all solid cancer mortality and incidence were not greatly affected when NIC subjects were excluded and all solid cancer deaths were restricted to those that occurred in Hiroshima and Nagasaki prefectures and PY were adjusted for probability of migration (Supplementary Table S2; https://doi.org/10.1667/RADE-21-00059.1.S1), although the magnitude of dose-response curvature among males in cancer mortality data increased.

Comparison of All Solid Cancer Mortality Risk Estimates with Report 14

To compare current risk estimates for solid cancer mortality with those of previous studies, we first repeated mortality analyses as in Report 14 while applying DS02R1 doses (*3*). Under these conditions (DS02R1, 1950–2003 follow-up, NIC subjects excluded) and the Ozasa et al. ERR model (stratified background, effect modification by sex, common attained age, age at exposure, no modification by high dose, and no adjustment for smoking), as previously (*3*), there was no indication of dose-response curvature over the full range of doses either among males or females (Supplementary Table S3, row 1; https://doi.org/10.1667/RADE-21-00059.1.S1). Then, in sensitivity analyses, we evaluated the effect of changing one condition or model parametrization at a time (Supplementary Table S3, rows 2–10) in the direction of the Grant et al. model (*7*). We found that each modification of the Report 14 model towards all solid cancer incidence model led to incremental reduction of AIC and improved description of cancer mortality data (Supplementary Table S3, rows 2–6). Changing from stratified to parametric background, adjusting for smoking, and other modifications in the model were largely inconsequential on estimates of dose-response parameters except for high dose adjustment. Allowing dose-response parameters for each sex to vary for subjects with total shielded kerma ≤ 4 Gy and >4 Gy resulted in lower linear ERR estimate and higher quadratic ERR estimate (i.e., enhanced curvature) among both males and females (Supplementary Table S3, row 4). Richer models to control for the high dose effect as well as excluding individuals

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TABLE 2
Linear Excess Relative Risk and Effect Modification Estimates for All Solid Cancer Mortality and Incidence: LSS, 1958–2009

	ERR/Gy						
	Sex-averaged	Males	Females	F:M ratio	Age at exposure, percentage change per decade	Attained age, power	
						Males	Females
	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI
Mortality[a]	0.44[b]	0.28	0.60	2.10	–16.76	–2.47	–1.33
	0.35 to 0.54	0.18 to 0.40	0.46 to 0.74	1.41 to 3.33	–27.41 to –5.62	–3.55 to –1.34	–2.08 to–0.54
Incidence[a]	0.46	0.28	0.64	2.31	–20.66	–2.54	–1.37
	0.38 to 0.54	0.19 to 0.38	0.52 to 0.77	1.66 to 3.37	–28.90 to –12.02	–3.39 to –1.68	–1.88 to –0.86

Notes. LSS, Life Span Study. ERR/Gy, excess relative risk per 1 Gy. 95% CI, confidence interval.

[a] Data are for the same individuals (i.e., NIC individuals included, individuals with missing doses excluded, those who died or were diagnosed with cancer prior to January 1, 1958 excluded). Mortality case series are for entire Japan while incidence case series include cases diagnosed in Hiroshima and Nagasaki prefectures and exclude ''autopsy only'' cases.

[b] All estimates are from linear ERR model with parametric background, multiplicative adjustment for smoking, independent effect modification by sex, sex-specific attained age, age at exposure, and high dose. The ERR estimates per 1 Gy are for survivors at age 70 exposure at age 30.

with total shielded kerma >4 Gy (n = 251, mean weighted colon dose of 2.61 Gy, range between 2.15 and 3.39 Gy) had little additional impact on sex-specific linear and quadratic ERR estimates for all solid cancer mortality (1958–2009 and 1950–2003 follow-up) or incidence (Supplementary Table S4; https://doi.org/10.1667/RADE-21-00059.1.S1).

Dose-Response Analyses in the Restricted Dose Ranges

We then applied the preferred all solid cancer incidence model (*7*) to examine dose-response curvature in the restricted dose ranges for the 1958–2009 period (Table 4). We found evidence of upward curvature in dose response for solid cancer mortality in the 0-2 Gy range among both males (P = 0.039) and females (P = 0.002). As in Grant et al. (*7*), evidence of male dose-response curvature for solid cancer incidence was apparent down to 0–1 Gy (P = 0.002) and there was no evidence of upward curvature in dose response among females at any dose range. For males, the patterns of linear ERR per Gy estimates for solid cancer mortality and incidence were not entirely monotonic as the dose range used for parameter estimation was reduced: decreasing down to the 0–0.25 Gy range and increasing in the 0–0.1 Gy range. For females, by contrast, the linear ERR per Gy estimates decreased monotonically at successively lower dose ranges for cancer mortality and were generally stable for cancer incidence. As the dose range narrowed, the precision of sex-specific ERR per Gy estimates for both solid cancer mortality and incidence decreased (i.e., 95% CI widen), reflecting loss of statistical power.

Figure 3 presents the sex-specific linear ERR per Gy estimates (95% CI) for solid cancer mortality (Fig.3A for females and Fig. 3C for males) and incidence (Fig. 3B for females and Fig. 3D for males) derived in the restricted dose ranges (from 0 to the values indicated on the horizontal axis). The solid black squares represent the ERR per Gy

TABLE 3
Excess Relative Risk Estimates for All Solid Cancer Mortality and incidence Under Linear-Quadratic Dose-Response Model: LSS, 1958–2009

	Mortality[a]				Incidence[a]			
	L	Q	Q/L		L	Q	Q/L	
Sex	95% CI	95% CI	95% CI	P[b]	95% CI	95% CI	95% CI	P[b]
Males	0.10[c]	0.12	1.24		0.08	0.12	1.58	
	–0.07 to 0.29	0.02 to 0.23	≤–2.99 or ≥0.07	0.062	–0.04 to 0.22	0.05 to 0.21	≤–5.08 or ≥0.26	0.001
Females	0.28	0.23	0.84		0.56	0.06	0.11	
	0.05 to 0.53	0.07 to 0.41	0.15 to 7.76	0.010	0.38 to 0.75	–0.05 to 0.18	–0.07 to 0.43	0.624
P[d]			0.781				0.017	

Notes. Life Span Study. ERR, excess relative risk. L, linear dose coefficient. Q, quadratic dose coefficient. Q/L, ratio of quadratic to linear dose coefficient or curvature. 95% CI, confidence interval.

[a] Data are for the same individuals (i.e., NIC individuals included, individuals with missing doses excluded, those who died or were diagnosed with cancer prior to January 1, 1958 excluded). Mortality case series are for entire Japan while incidence case series include cases diagnosed in Hiroshima and Nagasaki prefectures and exclude ''autopsy only'' cases.

[b] P value for quadratic departure from linearity.

[c] All estimates are from linear-quadratic ERR model with parametric background, multiplicative adjustment for smoking, independent effect modification by sex, sex-specific attained age, age at exposure, and high dose. The estimates are for survivors at age 70 after exposure at age 30.

[d] P value for heterogeneity in curvature by sex.

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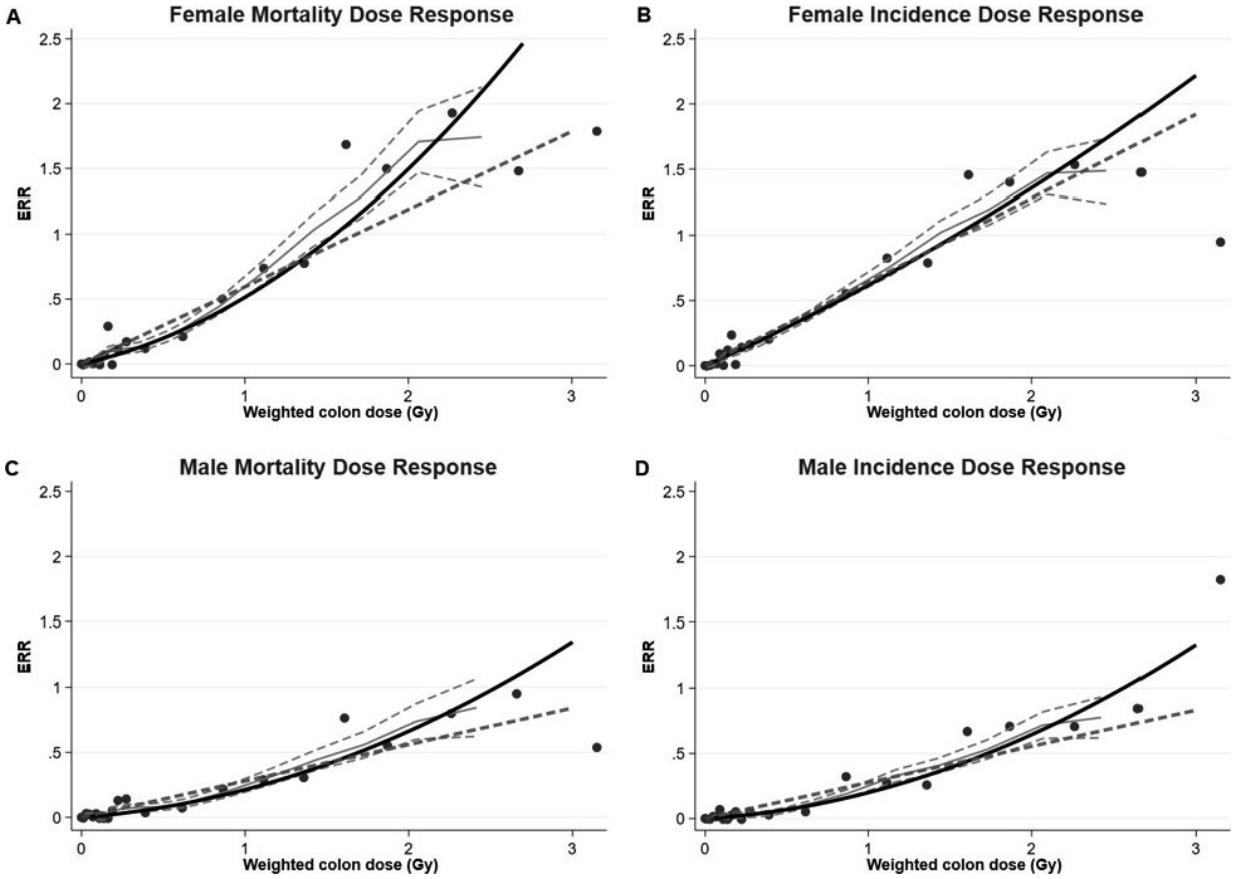


FIG. 2. All solid cancer mortality and incidence dose responses for males and females (full dose range) in the LSS, 1958–2009. Shown are categorical excess relative risk (ERR) points (black circles), fitted linear-quadratic (thick-black solid lines) and linear dose-response functions (thick-gray dashed lines), and nonparametric smoothed estimates (thin-gray solid lines) with pointwise 95% confidence intervals (thin-gray dashed lines) for females (panels A and B) and males (panels C and D). The ERR are shown for subjects at attained age 70 after exposure at age 30 years.

estimates based on the current data (1958–2009 follow-up with the NIC group included) and model. The cancer mortality plots also include the ERR per Gy estimates, indicated by hatched squares, based on the Report 14 data (1950–2003 follow-up without the NIC group) and model. For the low dose ranges ($\leq$0.25 Gy), the ERR per Gy estimates are quite uncertain. Comparing the all solid cancer mortality risk estimates for the current data and model to those using the Report 14 data and model given the same doses (DS02R1) we see that, while the confidence intervals overlap, the pattern of point estimates in the low dose ranges differs markedly, especially among females for whom the dose-response estimates decrease using the current data and model but increase when using the Report 14 data and model.

In further analyses of cancer mortality data over restricted dose ranges, we found that choice of a model (Supplementary Table S5, rows 1–9; https://doi.org/10.1667/RADE-21-00059.1.S1) and follow-up period (Supplementary Table S5, rows 9–12) each contributed to the apparent difference in patterns of estimated ERR per Gy in the low dose ranges (Supplementary Table S5 and Fig. S1; https://doi.org/10.1667/RADE-21-00059.1.S1). The current female ERR per Gy estimate in the 0–0.1 Gy range is lower than the 1950–2003 estimate by 93% and the male estimate is lower by 64%; also, their 95% CI include zero (Supplementary Table S5, rows 1–12; https://doi.org/10.1667/RADE-21-00059.1.S1). Approximately 73% of the difference in the ERR per Gy estimates among females was explained by the model and 27% by the extended follow-up (i.e., from 2003 to 2009); the corresponding proportions among males were 69% and 31%, respectively (Supplementary Table S5 and Fig. S1; https://doi.org/10.1667/RADE-21-00059.1.S1). Inclusion of the NIC subjects, beginning cancer mortality follow-up in 1958, and restricting analysis to the same subjects as in cancer incidence, had little additional effect on sex-specific estimates of linear ERR per Gy. As with the full range of doses, the current ERR model described all solid cancer mortality data in the 0-0.1 Gy better than the Report 14 model (AIC of 96403.86 vs. 97807.99, respectively).

Dose-Response Analyses by Calendar Period of Follow-Up and Age at Exposure

Table 5 summarizes the results of dose-response analyses for all solid cancer mortality according to calendar period of

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TABLE 4
Excess Relative Risk Estimates Over Selected Dose Ranges for All Solid Cancer Mortality and Incidence Under Linear and Linear-Quadratic Dose-Response Models: LSS, 1958–2009

Weighted colon dose,	Linear model				Linear–quadratic model									
	Males		Females		Males					Females				
Gy	L	95% CI	L	95% CI	L	95% CI	Q	95% CI	P[a]	L	95% CI	Q	95% CI	P[a]
Mortality[b]														
Full range	0.28[c]	0.18 to 0.40	0.60[c]	0.46 to 0.74	0.10[d]	–0.07 to 0.29	0.12[d]	0.02 to 0.23	0.062	0.28[d]	0.05 to 0.53	0.23[d]	0.07 to 0.41	0.010
0–2	0.27	0.16 to 0.39	0.57	0.43 to 0.73	0.05	<–0.14 to 0.27	0.16	0.01 to 0.32	0.039	0.17	–0.08 to 0.45	0.34	0.13 to 0.57	0.002
0–1	0.19	0.07 to 0.35	0.43	0.27 to 0.61	–0.005	<–0.29 to 0.32	0.25	–0.13 to >0.64	0.204	0.11	–0.29 to 0.54	0.45	–0.11 to 1.00	0.117
0–0.5	0.15	<–0.05 to 0.40	0.37	0.12 to 0.66	–0.13	<–0.38 to 0.42	0.75	<–0.60 to >2.13	0.289	–0.17	–0.83 to 0.59	1.38	–0.42 to 3.13	0.135
0–0.25	0.06[e]	<–0.34 to 0.49	0.25[e]	<–0.20 to 0.76	Parameter estimates were unstable due to limited data, results are not shown									
0–0.1	0.27	<–0.44 to 1.09	0.11	–0.94 to 1.28										
Incidence[b]														
Full range	0.28	0.19 to 0.38	0.64	0.52 to 0.77	0.08	–0.04 to 0.22	0.12	0.05 to 0.21	<0.001	0.56	0.38 to 0.75	0.06	–0.05 to 0.18	0.624
0–2	0.26	0.17 to 0.36	0.65	0.52 to 0.78	0.02	<–0.11 to 0.17	0.18	0.08 to 0.30	<0.001	0.48	0.28 to 0.69	0.14	–0.01 to 0.30	0.083
0–1	0.19	0.10 to 0.31	0.58	0.44 to 0.73	–0.10	<–0.11 to 0.09	0.41	0.15 to >0.63	0.002	0.48	0.19 to 0.80	0.13	–0.27 to 0.53	0.552
0–0.5	0.07	<–0.06 to 0.22	0.52	0.33 to 0.74	0.004	<–0.32 to 0.36	0.18	<–0.70 to >1.12	0.690	0.50	0.001 to 1.06	0.06	–1.33 to 1.39	0.930
0–0.25	0.02	<–0.19 to 0.25	0.55	0.23 to 0.91	Parameter estimates were unstable due to limited data, results are not shown									
0–0.1	0.32	<–0.12 to 0.85	0.40	–0.25 to 1.15	The model did not converge									

Notes. LSS, Life Span Study. ERR, excess relative risk. L, linear dose coefficient. Q, quadratic dose coefficient. 95% CI, confidence interval.

[a] P value for quadratic departure from linearity.

[b] Data are for the same individuals (i.e., NIC individuals included, individuals with missing doses excluded, those who died or were diagnosed with cancer prior to January 1, 1958 excluded). Mortality case series are for entire Japan while incidence case series include cases diagnosed in Hiroshima and Nagasaki prefectures and exclude ''autopsy only'' cases.

[c] ERR per 1 Gy estimates are from linear ERR models with parametric background, multiplicative adjustment for smoking, independent effect modification by sex, sex-specific attained age, age at exposure, and high dose. Estimates in the restricted dose ranges are derived using data for the entire cohort (see details in Materials and Methods). Estimates are shown for individuals at age 70 after exposure at age 30.

[d] ERR estimates are from linear-quadratic ERR models with parametric background, multiplicative adjustment for smoking, independent effect modification by sex, sex-specific attained age, age at exposure, and high dose. Estimates in the restricted dose ranges are derived using data for the entire cohort (see details in Materials and Methods). Estimates are shown for individuals at age 70 after exposure at age 30.

[e] The same model as in [c] except for common to males and females modification by attained age.

follow-up (1958–1987 vs. 1988–2009) and age at exposure (20–83 vs. 0–19). Due to inverse correlation between age at exposure and time since exposure in the LSS (correlation coefficient of 0.67 among individual survivors with solid cancer), most information accumulated during early follow-up came from those exposed in adulthood, while more recent information is increasingly influenced by those exposed during childhood. The ERR models in which sex-specific curvature was allowed to vary by calendar period or age at exposure described cancer mortality data equally well (AIC of 120645.97 vs. 120646.85, respectively). The estimates of dose-response curvature for each sex were markedly increased and significantly different from null in the later calendar period and among those exposed as children. The estimates of dose-response curvature for the early calendar period and those exposed in adulthood were not different from zero either among males or females. Tests of heterogeneity in sex-specific dose-response curvature by period or age at exposure were not significant (Table 5).

The results of dose-response analyses for all solid cancer incidence according to calendar period of follow up and age at exposure are summarized in Table 6. As with all solid cancer mortality, we could not discriminate between the models allowing for calendar period-specific or age-at-exposure-specific dose-response curvature (AIC of 64833.53 vs. 64832.86, respectively). Also similar to cancer mortality, the estimates of dose-response curvature for cancer incidence among males were noticeably and significantly elevated in the recent calendar period and among survivors exposed during childhood. By contrast to cancer mortality data, the estimates of dose-response curvature among males in cancer incidence data were also significantly elevated during the early period of follow-up while among females the estimates of dose-response curvature in both calendar periods and age at exposure groups were close to null. Neither male nor female difference in dose-response curvature by period or age at exposure was significant (Table 6).

To explore temporal patterns of dose-response curvature further, we fitted models allowing the dose-response parameters to vary jointly according to calendar period and age at exposure (Supplementary Table S6; https://doi.org/10.1667/RADE-21-00059.1.S1). These models had eight additional parameters compared to the models with either period- or age-at-exposure-specific curvature and did not describe cancer mortality or incidence data substantially better ($P \geq 0.488$ for cancer mortality and $P \geq 0.339$ for cancer incidence). Among survivors exposed during childhood, the estimates of dose-response curvature for each outcome were markedly increased among males in both calendar periods and among females in the recent calendar period. Among survivors exposed during adulthood (both males and females), there was little evidence of dose-response curvature for either outcome in any period.

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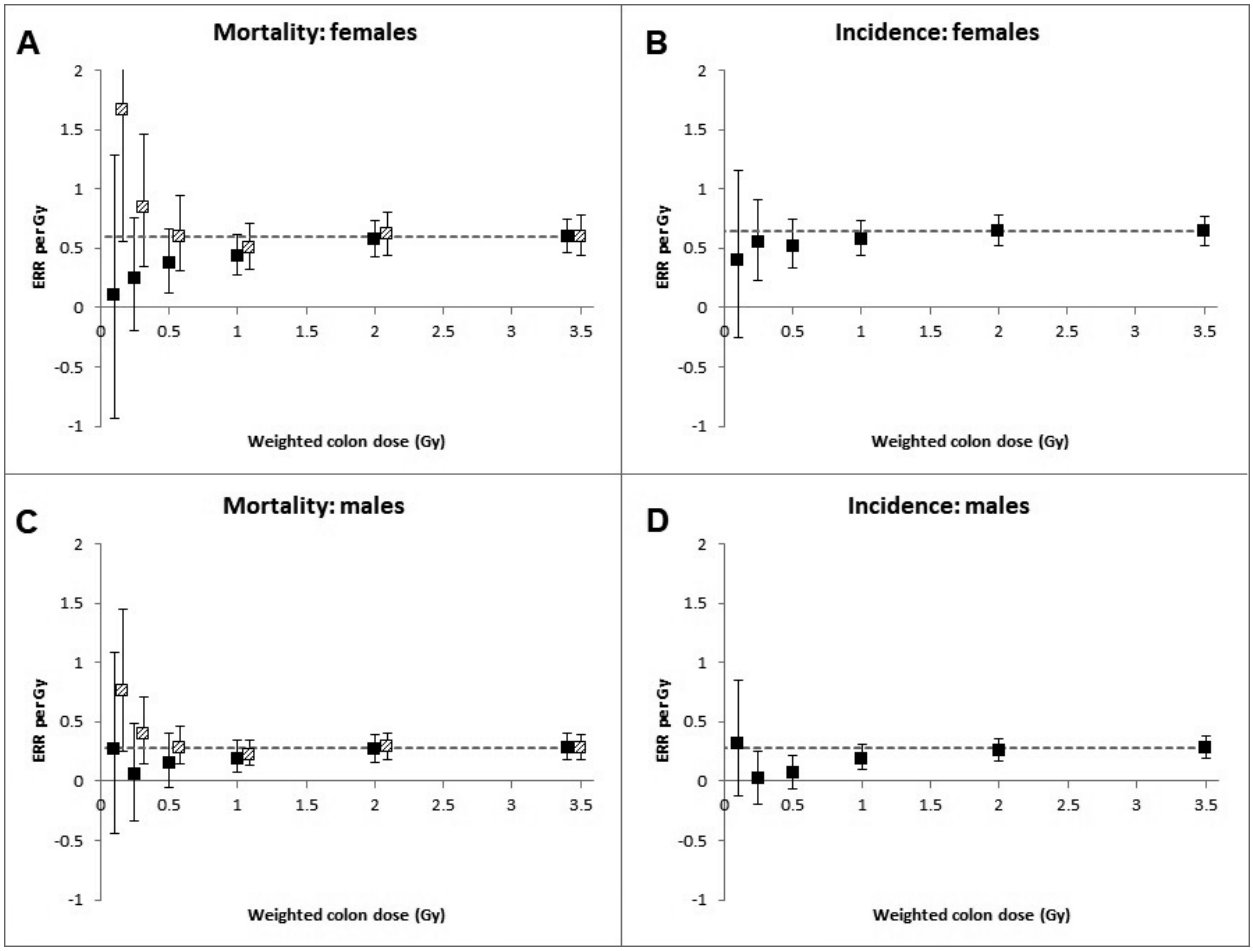


FIG. 3. Linear excess relative risk estimates (ERR) and 95% confidence intervals for all solid cancer mortality and incidence over selected dose ranges. The Y-axis is the excess relative risk per 1 Gy; the X-axis is the weighted colon dose in Gy. Black squares are the ERR per 1 Gy estimates for all solid cancer mortality and incidence for 1958–2009 period under the current dose-response model and inclusion criteria (see details in Materials and Methods). Hatched squares are the ERR per 1 Gy estimates for all solid cancer mortality for 1950–2003 period under the Report 14 model and inclusion criteria (see details in Materials and Methods). Vertical-black lines with horizontal caps indicate the 95% confidence intervals. The points for dose range up to 3.5 Gy and dashed lines represent the ERR per 1 Gy for the entire dose range with no segmentation in the dose response.

Composition of All Solid Cancers in Mortality and Incidence Data by Calendar Period

Comparative distributions of all solid cancers by site, sex, calendar period (1958–1987 vs. 1988–2009) within three attained age groups ($<$60, 60–79 and $\geq$80 years) in mortality and incidence data are shown in Supplementary Tables S7 and S8 (https://doi.org/10.1667/RADE-21-00059.1.S1), respectively. Overall, the contribution of stomach cancer deaths to all solid cancer mortality during the recent calendar period declined by 48% among males and 50% among females and contribution of colon, lung, and liver cancer deaths rose by 63% among males and 76% among females. Also, the proportion of breast cancer deaths during the recent period increased by 31% among females and the proportion of genital cancer deaths decreased by 47%. The above-described changes in the structure of solid cancer mortality were observed in all age-at-death groups. The temporal changes in composition of all solid cancers in incidence data were generally similar to those observed in mortality data (i.e., decreasing proportion of stomach and female genital cancers, and increasing proportion of colon, liver, lung, and female breast cancers in 1988–2009), although these changes were not seen consistently across all age-at-cancer diagnosis groups. An increase in the proportion of prostate cancer during the recent calendar period was more dramatic in male cancer incidence (246%) than cancer mortality data (63%) and occurred in all age groups.

Joint Analysis of Stomach, Colon, Liver, and Lung Cancer Mortality

To evaluate whether the dose-response curvature for the combined outcome could be related to unaccounted heterogeneity in background rates of individual cancer sites, we investigated the dose response for mortality from four common cancers: stomach, colon, liver, and lung, which collectively accounted for 68% of solid cancer deaths

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TABLE 5
Excess Relative Risk Estimates for All Solid Cancer Mortality by Calendar Period or Age at Exposure Under Linear-Quadratic Dose-Response Model: LSS, 1958–2009

Calendar period				Age at exposure			
		Q/L				Q/L	
Year	Deaths	95% CI	P[a]	Age	Deaths	95% CI	P[a]
Males							
1958–1987	3,731	0.29[b]	0.805	20–83	4,578	–0.04	0.648
		Undefined				–0.35 to 4.53	
1988–2009	3,793	5.99	0.024	0–19	2,946	7.88	0.015
		≤–1.54 or ≥0.18				NE or ≥0.23	
P[c]		0.425				0.108	
Females							
1958–1987	3,885	0.22	0.643	20–83	6,010	0.28	0.583
		–0.13 to 1.71				–0.13 to 3.21	
1988–2009	4,010	4.97	0.003	0–19	1,885	1.99	0.006
		≤–2.31 or ≥0.38				≤–4.00 or ≥0.26	
P[c]		0.063				0.186	

Notes. LSS, Life Span Study. ERR, excess relative risk. L, linear dose coefficient. Q, quadratic dose coefficient. Q/L, ratio of quadratic to linear dose coefficient or curvature. 95% CI, confidence interval. NE, not estimable.

[a] P value for quadratic departure from linearity.

[b] Curvature estimates are from linear-quadratic ERR models with parametric background (common to both calendar periods or ages at exposure), multiplicative adjustment for smoking, independent effect modification by sex, sex-specific attained age, age at exposure, and high dose.

[c] P value for heterogeneity in sex-specific curvature by calendar period or age at exposure.

(62% of incident cases) among males and 53% of solid cancer deaths (46% of incident cases) among females during the 1958–2009 period (Fig. 1). Their contribution to all solid cancers as a group substantially changed over time (described above). The results of joint endpoint dose-response analyses are presented in Table 7. When all model parameters fitted to four cancer site mortality were common, the magnitude and evidence for upward dose-response curvature among males was weaker and, among females, stronger than that for all solid cancer mortality. Allowing for site-specific baseline, smoking parameters, or site-period-specific baseline and smoking parameters drastically improved the model fit, but had no appreciable effect on dose-response estimates for the combined outcome either

TABLE 6
Excess Relative Risk Estimates for All Solid Cancer Incidence by Calendar Period or Age at Exposure Under Linear-Quadratic Dose-Response Model: LSS, 1958–2009

Calendar period				Age at exposure			
		Q/L				Q/L	
Year	Cases	95% CI	P[a]	Age	Cases	95% CI	P[a]
Males							
1958–1987	4,878	2.34[b]	0.031	20–83	5,628	0.16	0.891
		≤–1.25 or ≥0.12				Undefined	
1988–2009	5,595	1.52	0.022	0–19	4,845	2.43	<0.001
		≤–3.16 or ≥0.13				≤–3.23 or ≥0.33	
P[c]		0.845				0.258	
Females							
1958–1987	6,053	0.04	0.850	20–83	8,220	–0.02	0.573
		–0.14 to 0.40				–0.21 to 0.41	
1988–2009	6,012	0.23	0.373	0–19	3,845	0.20	0.273
		–0.07 to 1.06				–0.05 to 0.75	
P[c]		0.388				0.294	

Notes. LSS, Life Span Study. ERR, excess relative risk. L, linear dose coefficient. Q, quadratic dose coefficient. Q/L, ratio of quadratic to linear dose coefficient or curvature. 95% CI, confidence interval.

[a] P value for quadratic departure from linearity.

[b] Curvature estimates are from linear-quadratic ERR models with parametric background (common to both calendar periods or ages at exposure), multiplicative adjustment for smoking, independent effect modification by sex, sex-specific attained age, age at exposure, and high dose.

[c] P value for heterogeneity in sex-specific curvature by calendar period or age at exposure.

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TABLE 7
Excess Relative Risk Estimates for Mortality from Stomach, Colon, Liver, and Lung Cancers Combined in Relation to Weighted Colon Dose from the Joint Endpoint Analysis: LSS, 1958–2009

	Males				Females				
	L	Q			L	Q			
Model parameters	95% CI	95% CI	Q/L	P[a]	95% CI	95% CI	Q/L	P[a]	ΔAIC
Common to all sites	0.13[b] –0.08 to 0.38	0.08[b] –0.04 to 0.23	0.64	0.487	0.14 –0.19 to 0.50	0.31 0.08 to 0.55	2.11	0.016	0
Site-specific background	0.13[c] –0.09 to 0.38	0.09[c] –0.04 to 0.24	0.71	0.451	0.15 –0.19 to 0.51	0.30 0.07 to 0.55	2.00	0.018	1375.5
Site-specific smoking	0.13[d] –0.09 to 0.38	0.09[d] –0.04 to 0.23	0.66	0.480	0.14 –0.20 to 0.49	0.31 0.08 to 0.55	2.22	0.016	483.3
Site-specific background and smoking	0.13[e] –0.09 to 0.38	0.09[e] –0.04 to 0.24	0.70	0.463	0.14 –0.20 to 0.50	0.31 0.08 to 0.55	2.19	0.016	1624.9
Site-period-specific background and smoking[f]	0.14[f] –0.08 to 0.39	0.08[f] –0.04 to 0.22	0.57	0.544	0.11 –0.22 to 0.45	0.31 0.09 to 0.56	2.82	0.010	1765.8

Notes. LSS, Life Span Study. ERR, excess relative risk. L, linear dose coefficient. Q, quadratic dose coefficient. Q/L, ratio of quadratic to linear dose coefficient or curvature. 95% CI, confidence interval. AIC, Akaike information criterion.

[a] P value for quadratic departure from linearity.

[b] Estimates are from the linear-quadratic ERR model adjusted for multiplicity of data with common (to all sites) parametric background, common (to all sites) multiplicative adjustment for smoking and common (to all sites) effect modification (by sex, sex-specific attained age, age at exposure, and high dose). Estimates are shown for individuals at age 70 after exposure at age 30. This analysis is equivalent to standard analysis of the combined outcome using a single PY table (see details in Materials and Methods).

[c] Estimates are from the linear-quadratic ERR model adjusted for multiplicity of data with site-specific background parameters, common (to all sites) multiplicative adjustment for smoking and common (to all sites) effect modification (by sex, sex-specific attained age, age at exposure, and high dose). Estimates are shown for individuals at age 70 after exposure at age 30 (see details in Materials and Methods).

[d] Estimates are from the linear-quadratic ERR model adjusted for multiplicity of data with common (to all sites) parametric background, site-specific multiplicative adjustment for smoking and common (to all sites) effect modification (by sex, sex-specific attained age, age at exposure, and high dose). Estimates are shown for individuals at age 70 after exposure at age 30 (see details in Materials and Methods).

[e] Estimates are from the linear-quadratic ERR model adjusted for multiplicity of data with site-specific parametric background, site-specific multiplicative adjustment for smoking and common (to all sites) effect modification (by sex, sex-specific attained age, age at exposure, and high dose). Estimates are shown for individuals at age 70 after exposure at age 30 (see details in Materials and Methods).

[f] Estimates are from the ERR model adjusted for multiplicity of data with site-period-specific parametric background (separate parameters for 1958–1987 and 1988–2009 for each site), site-period-specific multiplicative adjustment for smoking (separate parameters for 1958–1987 and 1988–2009 for each site) and common (to all sites and both calendar periods) effect modification (by sex, sex-specific attained age, age at exposure and high dose). Estimates are shown for individuals at age 70 after exposure at age 30 (see details in Materials and Methods).

among males or females (Table 7). In site-specific analyses (Table 8), we found that the estimate of dose-response curvature was elevated for stomach cancer mortality among males and for liver cancer mortality among females, although not significantly so. While linear-quadratic models for colon cancer mortality failed to converge for either males or females due to the magnitude of the linear dose coefficient, there were no problems in fitting linear or pure-quadratic dose-response models (i.e., linear dose coefficient constrained to be zero). The pure quadratic model described the data somewhat better than the linear model ($P = 0.091$ for males and $P = 0.025$ for females).

DISCUSSION

Until recently, there was little evidence against linearity in dose response for all solid cancer mortality or incidence in the LSS (*5, 6, 8, 23, 24*). However, the most recent cancer mortality and incidence reports found evidence of a modest upward curvature in dose response among males and less consistent evidence of a similar curvature among females in the 0–2 Gy dose range (*3, 7, 9*). To develop a better understanding of the emerging dose-response pattern, we compared the sex-specific dose-response shape in the LSS for all solid cancer mortality and incidence. We minimized methodological differences between mortality and incidence studies by extending mortality follow-up through 2009 (but restricting it to 1958–2009) and applying DS02R1 doses (*9*), including NIC, and using smoking-adjusted risk models of the form considered in the analyses of cancer incidence data in Grant et al. (*3*). Under these conditions, solid cancer mortality dose-response estimated over the entire range of doses exhibited a significant upward curvature among females. The male mortality curvature, nearly statistically significant, was consistent with solid cancer incidence data, but the female mortality curvature was inconsistent with the female incidence dose response that followed a linear function. The results of solid cancer mortality analyses in

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TABLE 8
Site-Specific Excess Relative Risk Estimates for Cancer Mortality in Relation to Weighted Colon Dose Under Linear and Linear-Quadratic Dose-Response Models: LSS, 1958-2009

	Males						Females					
		L	L	Q				L	L	Q		
Site	N	95% CI	95% CI	95% CI	Q/L	P[a]	N	95% CI	95% CI	95% CI	Q/L	P[a]
Stomach	2,105	0.12[b]	0.03[c]	0.04[c]	1.72	0.487	1,790	0.43[b]	0.45[c]	–0.01[c]	–0.01	0.792
		<–0.01 to 0.31	<–0.03 to 0.38	NE				0.19 to 0.73	–0.06 to >1.01	NE		
Colon	396	0.52	0[d]	0.40[d]	Infinite	0.091[e]	605	0.39	0[d]	0.38[d]	Infinite	0.025[e]
		0.15 to 1.13		0.14 to 0.82				0.09 to 0.87		0.11 to 0.80		
Liver	1,120	0.26	0.26	–0.01	–0.04	0.930	806	0.40	0.11	0.28	2.58	0.204
		0.04 to 0.58	<0.05 to 0.83	<–0.27 to 0.31				0.09 to 0.82	<–0.59 to 0.73	–0.13 to 0.94		
Lung	1,488	0.42	0.32	0.06	0.19	0.883	1,004	1.03	0.71	0.21	0.29	0.508
		0.16 to 0.72	<–0.23 to 0.95	<–0.28 to 0.43				0.57 to 1.61	<–0.12 to 1.62	<–0.34 to 0.80		

Notes. LSS, Life Span Study. N, number of deaths. ERR, excess relative risk. L, linear dose coefficient. Q, quadratic dose coefficient. Q/L, ratio of quadratic to linear dose coefficient or curvature. 95% CI, confidence interval. AIC, Akaike information criterion.

[a] P value for quadratic departure from linearity unless stated otherwise.

[b] Estimates are from the site-specific linear ERR models with parametric background, multiplicative adjustment for smoking, and independent effect modification by sex, sex-specific attained age, age at exposure, and high dose. Estimates are shown for individuals at age 70 after exposure at age 30.

[c] Estimates are from the site-specific linear-quadratic ERR models with parametric background, multiplicative adjustment for smoking, and independent effect modification by sex, sex-specific attained age, age at exposure, and high dose unless stated otherwise. Estimates are shown for individuals at age 70 after exposure at age 30.

[d] Estimates are from site-specific pure quadratic ERR model (i.e., linear dose coefficient constrained to be zero) with parametric background, multiplicative adjustment for smoking, and independent effect modification by sex, sex-specific attained age, age at exposure and high dose. Estimates are shown for individuals at age 70 after exposure at age 30.

[e] With linear dose coefficient constrained to be zero.

the 0–2 Gy dose range and over the entire follow-up (i.e., 1950–2009) were similar, revealing significant upward curvature in dose response for each sex. Patterns of sex-specific curvature by calendar period (1958–1987 vs. 1988–2009) and age at exposure (0–19 vs. 20–83) varied between mortality and incidence data, particularly for females, although for each outcome there was an indication of curvature among 0–19-year-old male survivors in both calendar periods and among 0–19-year-old female survivors in the recent period.

We found that the preferred ERR model for all solid cancer incidence described cancer mortality data better than the Report 14 model (*3*) over the entire range of doses; there was an incremental AIC reduction in all solid cancer mortality models from applying parametric rather than stratified baseline, adjusting for smoking, and allowing for separate (rather than common) trend in ERR with attained age among males and females. As with all solid cancer incidence data (*7*), adjustment for smoking had no impact on the magnitude or shape of the dose response for all solid cancer mortality either among males or females, reflecting little association between smoking behavior and radiation exposure in the LSS (*15, 16, 25*). Another difference from the Report 14 model was that we adjusted for ''high dose'' effect. This indicator was included to minimize the influence of individuals with total shielded kerma >4 Gy, who have considerable uncertainties in their dose estimates, on the dose-response parameters. Unlike other modifications to the cancer mortality model, this adjustment substantially enhanced the magnitude of upward curvature in the dose response for each sex. Considerable evidence of dose-response curvature for all solid cancer mortality was also found in recent reanalysis of Report 14 data by Little et al. under a different statistical model after survivors with untruncated, unadjusted weighted colon doses >3 Gy were excluded (*12*). This approach is similar to our method of separating survivors with total shielded kerma ≤4 Gy and >4 Gy in the model. The estimates of sex-specific curvature for solid cancer incidence also increased after adjustment for high dose, although to a lesser extent than those for cancer mortality. The influence of ''high dose'' survivors on estimation of dose response for all solid cancer is related to the fact that there appears to be a downturn in dose response at very high doses. Whether the downturn is due to unaccounted dose error or cell killing continues to be debated. Collectively, these findings suggest that without allowance for high-dose effect our inference about the dose-response shape over the full range of doses in the LSS could be biased. However, it is important to recognize that substantial evidence of dose-response curvature for all solid cancer is present in the 0–2 Gy range, at doses associated with smaller uncertainties, in mortality data for males and females, and in incidence data for males.

The results of our analyses in the restricted dose ranges lend further insights to inferences made about all solid cancer dose-response shape over the entire range of doses. If the true dose response followed an upwardly curving linear-quadratic function, then the linear slope estimated in the restricted dose range would decrease as the dose range was narrowed down; if the true dose response was linear, then

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linear slopes estimated at lower dose ranges would be stable. In the main analyses (under the preferred ERR model), we did observe a decreasing pattern of linear ERR estimates at progressively lower dose ranges for female cancer mortality down to 0–0.1 Gy and for both male cancer mortality and incidence down to 0–0.25 Gy (Table 4). Subsequent increase of male ERR estimates per Gy in the 0–0.1 Gy range is not easy to interpret but may provide evidence for a positive dose-response slope at low doses. The current study results for all solid cancer mortality appear different from those of Ozasa et al. (*3*), in which, as the dose range decreased (0–<0.3 Gy), the sex-averaged linear ERR increased markedly. We reproduced the Report 14 pattern under DS02R1 doses and otherwise similar conditions and model and demonstrated that this pattern affected both sexes. We attributed much of the difference in the pattern and magnitude of sex-specific linear ERR estimates at low-dose ranges between the two studies to the use of a different statistical model (about 70% in the 0–0.1 Gy range), although extended follow-up contributed as well (about 30%).

Estimation of radiation risk at low doses was beyond the scope of our paper. This is a formidable challenge that requires advanced statistical methods to maximize statistical power and precision (*26, 27*). However, we made several useful observations. Unlike the sex-specific linear ERR estimates derived from the entire range of doses, the ERR per Gy estimates for all solid cancer mortality at low doses were sensitive to how the background rates were modeled and adjusted for (stratified vs. parametric, proximal vs. proximal and distal combined, smoking adjusted vs. not) and how the dose response at higher doses was controlled (linear-quadratic vs. linear above the cutpoint). The latter point is particularly important in view of the significant upward curvature in dose response observed in the current mortality data for both males and females. While our model provided an improved characterization of data in the 0–0.1 Gy range compared to the Report 14 model (*3*), it was optimized over the full range of doses. It has been pointed out that the potential for uncontrolled confounding at low doses is greater and this requires careful modeling of risk (*28*).

With the standardized approach applied to the analysis of all solid cancer mortality and incidence data, the difference in sex-specific patterns of dose-response curvature for two outcomes (i.e., male dose-response curvature in both cancer mortality and incidence data and female dose-response curvature in cancer mortality but not cancer incidence data) cannot be attributed to the use of different doses (DS02 vs. DS02R1), follow-up period (1950–2003 vs. 1958–2009), treatment of NIC subjects (excluded vs. included), or statistical models (Ozasa et al. vs. Grant et al.). Moreover, consistency of sex-specific patterns of curvature in standard analyses of cancer mortality data and analyses limited to cancer deaths occurring in Hiroshima and Nagasaki prefectures with PY adjusted for probability of migration (Supplementary Table S2; https://doi.org/10.1667/RADE-21-00059.1.S1), does not support the idea that sex-specific mortality, incidence differences in dose-response curvature could be related to differences in cases catchment area or migration adjustment. Consequently, the sex-specific patterns of dose response for all solid cancer appear to originate from the type of data analyzed (i.e., cancer death vs. incident cancer).

One of the main differences between all solid cancer mortality and incidence data concerns the composition of cases due to the variation in cancer-specific survival. Due to good survival, thyroid cancer, benign brain/CNS tumors (55% of all incident brain/CNS tumors in LSS), and sex-specific cancers (e.g., breast, prostate) have proportionally lower frequency in all solid cancer mortality data, particularly so for females. As these neoplasms exhibit strong linear dose response in incidence data (*29–32*), their deficit in the mortality data could unmask non-linearity in all solid cancer dose response arising from other cancer sites (if present). Our finding of the female upward curvature in cancer mortality, but not in cancer incidence dose response is consistent with this idea, and supports the finding of Cologne et al. that, after excluding thyroid and breast cancers from the analysis of all solid cancer incidence, the magnitude of female dose-response curvature for the remaining sites increased substantially (*10*). By contrast, the effect of cancers with good prognosis is not entirely consistent with the finding of male dose-response curvature, which is seen in both cancer mortality and incidence data. This may in part be due to the lower (compared to females) fraction of less fatal cancers in male all solid cancer incidence data, but there are other factors to consider since the effect of excluding thyroid cancer and brain/CNS neoplasms on male dose-response curvature for the remaining sites in cancer incidence data was opposite to that of excluding prostate cancer (*10*).

Aggregating all solid cancers in the LSS, and other studies of populations with whole body homogeneous exposure to ionizing radiation, has been performed to increase statistical power and precision of radiation risk estimates and to provide useful information for radiation protection purposes (*1, 33*). However, the disadvantage of this approach is that it assumes homogeneity and does not account for potential differences in baseline rates, magnitude and shape of dose response, or nature of effect modification across different cancer sites stemming from differences in etiology and sensitivity to carcinogenic effects of radiation and this could lead to non-linear dose response for the aggregated outcome. Grant et al. (*7*) and Cologne et al. (*10*) proposed and evaluated several sources of dose-response curvature for all solid cancer related to pooling data from multiple sites in cancer incidence data. Specifically, Grant et al. suggested that heterogeneity in dose-response shape across cancer sites, coupled with differential distribution of these sites by sex, could lead to a different magnitude of sex-specific dose-response curva-

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ture for the combined outcome (*7*); while Cologne et al. provided an example of how spurious dose-response curvature in incidence data could occur due to heterogeneity in the background rates that is not properly controlled when individual cancer sites are aggregated together (*10*). To evaluate these possibilities in cancer mortality data, we selected the four most common cancers in the LSS (i.e., stomach, colon, liver, and lung), collectively accounting for more than half of cancer deaths among males and females and conducted joint endpoint analysis. Contrary to our expectation, controlling for a noticeable site-specific heterogeneity in the background rates and smoking effects had little impact on estimates of sex-specific dose-response curvature in the joint endpoint analysis of four cancer site mortality whereas there was some evidence of heterogeneity in dose-response shape by site and sex. An upward dose-response curvature for colon cancer mortality in each sex and suggestive dose-response curvature for liver cancer mortality among females were unexpected as recent studies of colon and liver cancer incidence found no indication for lack of linear model fit (*34, 35*). The results of four cancer site mortality analyses do not invalidate the importance of proper control for site-specific heterogeneity in background rates because these findings could not be generalized to the remaining cancer sites. Rather, our experience underscores the importance of joint endpoint analyses in attributing dose-response curvature for all solid cancer to a particular site or cause (e.g., heterogeneity in background rates or dose response shapes).

One potential explanation for the emergence of all solid cancer dose-response curvature in recent LSS data (*3, 7*) is an increased number of radiation-related cases and statistical power to detect departure from linearity (if present). Another possibility is that the upward curvature is related to incompletely controlled temporal trends in the background rates and/or changing compositions of all solid cancers as a group or that it is a real time-dependent phenomenon. Our approach to evaluating changes in dose-response curvature over time (or age at exposure) was similar to that used previously (*20*). We used all solid cancer mortality and incidence data for the entire follow up period (or all ages at exposure) and fitted models allowing for sex-period-specific (or sex-age-at exposure-specific) dose-response parameters under common background parameters. While we failed to reject homogeneity of sex-specific curvature in dose response for all solid cancer mortality by calendar period or age at exposure, we found strong, statistically significant evidence of dose-response curvature in the later period and among those exposed during childhood for both males and females and no indication of curvature in the earlier period or those exposed in adulthood for either sex. These findings further in several ways the Ozasa et al. observation of increasing sex-averaged curvature in the ERR for cancer mortality with longer follow up (*3*). We demonstrated that the temporal trend in dose-response curvature continued as mortality follow-up was extended through 2009, affected both sexes, and survivors exposed during childhood. The period and age-at-exposure patterns of dose-response curvature in cancer incidence data were seemingly different (i.e., statistically significant male curvature observed in both calendar periods and lack of curvature in the female dose-response in either period or among those exposed during childhood). This inconsistency, particularly apparent for females, is surprising because the composition of all solid cancers in mortality and incidence data changed over time in a similar way (i.e., the proportion of stomach and female genital cancers in recent follow up period decreased, and the proportion of colon, liver, lung, and female breast cancers increased) implying that both outcomes are affected by common temporal trends. Interestingly, the sex-specific patterns of dose-response curvature in mortality and incidence data became more comparable in the exploratory analyses, when the dose-response parameters were allowed to vary jointly by calendar period and age at exposure. These analyses suggested an upward curvature in dose response for each outcome among 0–19-year-old male survivors in both calendar periods and among 0–19-year-old female survivors in the recent calendar period. Approximately 44% of the LSS members were less than 20 years old at the time of the bombing (*7*). These survivors belong to recent birth cohorts (1926–1945) which are more associated with a 'Westernized' lifestyle compared to cohorts born in earlier calendar years (*36, 37*). Their exposure to lifestyle-related risk factors most likely occurred after exposure to atomic bomb radiation. They also reached ages of usual cancer onset during a period of improved cancer diagnosis and prognosis. How precisely these factors might have interacted with radiation exposure and contributed to the emerging curvature in all solid cancer dose response remains unexplored. At the end of 2009, 84% of the LSS members exposed during childhood were alive compared to 15% of those exposed during adulthood (*7*). Further follow-up will be essential in establishing whether the dose-response curvature for all solid cancer among youngest survivors persists as well as unveiling potential contributing factors and cancer sites.

Several points need to be considered in interpreting the results of our study. Analyses were based on doses estimated by the latest dosimetry system (DS02R1) with improved location and terrain shielding data (*9*). As in previous studies of all solid cancer risk (*3, 6, 38*), we used weighted absorbed colon dose as the whole-body representative organ with assumed neutron RBE of 10. The colon dose is an appropriate surrogate for internally located organs (e.g., stomach, liver and lung). For superficially located organs (e.g., breast and thyroid), it is a suboptimal surrogate because neutron doses for these organs would be underestimated due to shielding of colon by overlaying tissues (*39, 40*). However, neutron doses comprise only a small fraction of overall absorbed organ doses, particularly in Nagasaki, with most survivors receiving less than 1 mGy of neutron

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doses (*39*). Also, a true RBE of neutrons remains highly uncertain. While the recent LSS study suggested that the traditionally assumed value of 10 may be an underestimate (*40*), the data-derived RBE had wide confidence bounds and was higher than the RBE estimated by experimental studies of animals and cell lines. Recent development of new computational voxel phantom series (*40*) opens a possibility for further improvements in LSS dosimetry, particularly neutron doses, and reevaluating dose-response shape in the future. The applied colon doses were adjusted for random errors assuming 35% coefficient of variation as proposed by Pierce et al. (*13*). Improved characterization of dose error (e.g., in ''high dose'' survivors, in relation to survivor's shielding, type of responder to dosimetry questionnaire) coupled with advanced statistical methods to control for it is another direction that may help to delineate the dose-response shape for all solid cancer. Cancer mortality data in the LSS are ascertained through a nationwide monitoring of death-certificates since 1950 (*2, 3*) while cancer incidence data are ascertained through regional cancer registries in Hiroshima and Nagasaki since 1958 (*4*). Consequently, PY used in the analysis of cancer incidence are adjusted for migration into and out of the cancer registries' catchment areas by applying city-, sex-, age- and calendar time-dependent residence probabilities estimated from the AHS data. Ascertainment of cancer from death certificate is less accurate than that from cancer registry and misclassification is possible between primary and secondary cancer, first primary and higher order primary cancer, or between cancer and non-cancer death. However, misattributing an underlying cause of death to a particular solid cancer when the true cause is a different cancer is unlikely to introduce bias because we evaluated deaths from all solid cancers together and, further, radiation ERR from atomic bombings for second or higher incident primary cancers in the LSS was shown to be comparable to that for first primary cancer (*41*). Misclassification between death from cancer and non-cancer is a more serious concern, particularly if related to dose (*42*). Previous LSS studies with a follow-up through 1987 demonstrated that up to 22% of cancers diagnosed at autopsy were missed on death certificates (*43*), but found no evidence of dose dependent misclassification (*44*). Strong evidence of mortality curvature among males and females in the recent calendar period characterized by improved medical diagnosis and reporting standards makes cause of death misclassification as an explanation for dose-response curvature less plausible. Smoking data were available for 60% of the LSS cohort. To maximize statistical power and minimize potential bias associated with exclusion of 40% of the cohort without smoking data (*45*), smoking status was treated in a time-dependent fashion with all subjects starting with an ''unknown'' status that was changed at the time smoking data became known. We did not assess dose-response curvature for all individual sites either in cancer mortality or incidence data. Nearly all site-specific analyses in the new LSS cancer incidence series have been completed, while detailed analyses of updated cancer mortality data will be conducted in the future, facilitating the attribution of all solid cancer dose-response curvature to a particular site or group of cancers.

In conclusion, we applied similar analytical methods and rate models to all solid cancer mortality and incidence data in the LSS and found consistent evidence of a modest upward dose-response curvature among males for each outcome. By contrast, the upward curvature of comparable magnitude among females was specific to all solid cancer mortality data. There was a suggestion of dose-response curvature for each outcome among survivors exposed to the atomic bomb during childhood or in the recent follow-up period. Collectively, our findings strengthen evidence that the upward curvature in all solid cancer dose response in the LSS is neither specific to males nor to cancer incidence; its evidence appears to depend on the composition of sites comprising all solid cancer group and age at exposure or time. Further follow-up and site-specific analyses of cancer incidence and mortality will be important to confirm the emerging trend in dose-response curvature among young survivors and unveil the contributing factors and sites.

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REFERENCES

1. United Nations. Scientific Committee on the Effects of Atomic Radiation. Effects of ionizing radiation : United Nations Scientific Committee on the Effects of Atomic Radiation: UNSCEAR 2006. New York: United Nations; 2008.
2. Ozasa K, Cullings HM, Ohishi W, Hida A, Grant EJ. Epidemiological studies of atomic bomb radiation at the radiation effects research foundation. Int J Radiat Biol 2019; 95(7):879-91.
3. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res 2012; 177(3):229-43.
4. Mabuchi K, Soda M, Ron E, Tokunaga M, Ochikubo S, Sugimoto S, et al. Cancer incidence in atomic bomb survivors. Part I: Use of the tumor registries in Hiroshima and Nagasaki for incidence studies. Radiat Res 1994; 137(2 Suppl):S1-16.
5. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid

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cancer and noncancer disease mortality: 1950-1997. Radiat Res 2003; 160(4):381-407.

6. 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):1-64.

7. Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, et al. Solid cancer incidence among the life span study of atomic bomb survivors: 1958-2009. Radiat Res 2017; 187(5):513-37.

8. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. Radiat Res 1994; 137(2 Suppl):S17-67.

9. Cullings HM, Grant EJ, Egbert SD, Watanabe T, Oda T, Nakamura F, et al. DS02R1: Improvements to atomic bomb survivors' input data and implementation of Dosimetry System 2002 (DS02) and resulting changes in estimated doses. Health Phys 2017; 112(1):56-97.

10. Cologne J, Kim J, Sugiyama H, French B, Cullings HM, Preston DL, et al. Effect of heterogeneity in background incidence on inference about the solid-cancer radiation dose response in atomic bomb survivors. Radiat Res 2019; 192(4):388-98.

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(1 Pt 2):219-54.

12. Little MP, Pawel D, Misumi M, Hamada N, Cullings HM, Wakeford R, et al. Lifetime Mortality risk from cancer and circulatory disease predicted from the Japanese atomic bomb survivor life span study data taking account of dose measurement error. Radiat Res 2020; 194(3):259-76.

13. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res 1990; 123(3):275-84.

14. Beebe GW, Fujisawa H, Yamasaki M. ABCC-JNIH Adult Health Study. Reference papers. 1. Selection of the sample. 2. Characteristics of the sample. ABCC-RERF; 1960. Report No.: TR 10-60.

15. Cahoon EK, Preston DL, Pierce DA, Grant E, Brenner AV, Mabuchi K, et al. Lung, Laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: An updated analysis from 1958 through 2009. Radiat Res 2017; 187(5):538-48.

16. Furukawa K, Preston DL, Lonn 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(1):72-82.

17. Sposto R, Preston DL. Correcting for catchment area nonresidency in studies based on tumor-registry data. Hiroshima: Radiation Effects Research Foundation; 1992. Report No.: CR 1-92.

18. French B, Cologne J, Sakata R, Utada M, Preston DL. Selection of reference groups in the Life Span Study of atomic bomb survivors. Eur J Epidemiol 2017; 32(12):1055-63.

19. Cologne JB, Preston DL. Longevity of atomic-bomb survivors. Lancet 2000; 356(9226):303-7.

20. Cologne J, Preston DL, Grant EJ, Cullings HM, Ozasa K. Effect of follow-up period on minimal-significant dose in the atomic-bomb survivor studies. Radiat Environ Biophys 2018; 57(1):83-8.

21. Pierce DA, Preston DL. Joint analysis of site-specific cancer risks for the atomic bomb survivors. Radiat Res 1993; 134(2):134-42.

22. Preston DL, Lubin JH, Pierce DA, McConney ME, Shilnikova NS. Epicure Risk Regression and Person-Year Computation Software: Command Summary and User Guide. Ottawa, ON, Canada: Risk Sciences International; 2015.

23. Ron E, Preston DL, Mabuchi K, Thompson DE, Soda M. Cancer incidence in atomic bomb survivors. Part IV: Comparison of cancer incidence and mortality. Radiat Res 1994; 137(2 Suppl):S98-112.

24. 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):1-27.

25. Utada M, Brenner AV, Preston DL, Cologne JB, Sakata R, Sugiyama H, et al. Radiation Risks of uterine cancer in atomic bomb survivors: 1958-2009. JNCI Cancer Spectr 2018; 2(4):pky081.

26. Furukawa K, Misumi M. A semiparametric approach to evaluate the harm of low-dose exposures. J Radiol Prot 2018; 38(1):286-98.

27. Gilbert ES, Little MP, Preston DL, Stram DO. Issues in interpreting epidemiologic studies of populations exposed to low-dose, high-energy photon radiation. J Natl Cancer Inst Monogr 2020; 2020(56):176-87.

28. Schubauer-Berigan MK, Berrington de Gonzalez A, Cardis E, Laurier D, Lubin JH, Hauptmann M, et al. Evaluation of confounding and selection bias in epidemiological studies of populations exposed to low-dose, high-energy photon radiation. J Natl Cancer Inst Monogr 2020; 2020(56):133-53.

29. Furukawa K, Preston D, Funamoto S, Yonehara S, Ito M, Tokuoka S, et al. Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. Int J Cancer 2013; 132(5):1222-6.

30. Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst 2002; 94(20):1555-63.

31. Brenner AV, Sugiyama H, Preston DL, Sakata R, French B, Sadakane A, et al. Radiation risk of central nervous system tumors in the Life Span Study of atomic bomb survivors, 1958-2009. Eur J Epidemiol 2020; 35(6):591-600.

32. Mabuchi K, Preston DL, Brenner AV, Sugiyama H, Utada M, Sakata R, et al. Risk of prostate cancer incidence among atomic bomb survivors: 1958-2009. Radiat Res 2021; 195(1):66-76.

33. National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, D.C.: National Academies Press; 2006. xvi, 406 p. p.

34. Sugiyama H, Misumi M, Brenner A, Grant EJ, Sakata R, Sadakane A, et al. Radiation risk of incident colorectal cancer by anatomical site among atomic bomb survivors: 1958-2009. Int J Cancer 2020; 146(3):635-45.

35. Sadakane A, French B, Brenner AV, Preston DL, Sugiyama H, Grant EJ, et al. Radiation and risk of liver, biliary tract, and pancreatic cancers among atomic bomb survivors in Hiroshima and Nagasaki: 1958–2009. Radiat Res 2019; 192(3):299-310.

36. Yoshiike N, Matsumura Y, Iwaya M, Sugiyama M, Yamaguchi M. National nutrition survey in Japan. J Epidemiol 1996; 6(3 Suppl):S189-200.

37. Gersten O, Wilmoth JR. The cancer transition in Japan since 1951. Demographic Res 2002; 7(5):271-306.

38. Brenner AV, Preston DL, Sakata R, Sugiyama H, de Gonzalez AB, French B, et al. Incidence of breast cancer in the Life span study of atomic bomb survivors: 1958-2009. Radiat Res 2018; 190(4):433-44.

39. Cordova KA, Cullings HM. Assessing the relative biological effectiveness of neutrons across organs of varying depth among the atomic bomb survivors. Radiat Res 2019; 192(4):380-7.

40. griffin k, paulbeck c, bolch w, cullings h, egbert s, funamoto s, et al. dosimetric impact of a new computational voxel phantom series for the Japanese atomic bomb survivors: Children and adults. Radiat Res 2019; 191(4):369-79.

41. Li CI, Nishi N, McDougall JA, Semmens EO, Sugiyama H, Soda M, et al. Relationship between radiation exposure and risk of second primary cancers among atomic bomb survivors. Cancer Res 2010; 70(18):7187-98.

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42. Sposto R, Preston DL, Shimizu Y, Mabuchi K. The effect of diagnostic misclassification on non-cancer and cancer mortality dose response in A-bomb survivors. Biometrics 1992; 48(2):605-17.

43. Jablon S, Thompson D, McConney M, Mabuchi K. Accuracy of cause-of-death certification in Hiroshima and Nagasaki, Japan. Ann N Y Acad Sci 1990; 609:100-9.

44. Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. Epidemiology 1994; 5(1):48-56.

45. Furukawa K, Preston DL, Misumi M, Cullings HM. Handling incomplete smoking history data in survival analysis. Stat Methods Med Res 2017; 26(2):707-23.

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