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Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009

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This is the third analysis of solid cancer incidence among the Life Span Study (LSS) cohort of atomic bomb survivors in Hiroshima and Nagasaki, adding eleven years of follow-up data since the previously reported analysis. For this analysis, several changes and improvements were implemented, including updated dose estimates (DS02R1) and adjustment for smoking. Here, we focus on all solid cancers in aggregate. The eligible cohort included 105,444 subjects who were alive and had no known history of cancer at the start of follow-up. A total of 80,205 subjects had individual dose estimates and 25,239 were not in either city at the time of the bombings. The follow-up period was 1958–2009, providing 3,079,484 person-years of follow-up. Cases were identified by linkage with population-based Hiroshima and Nagasaki Cancer Registries. Poisson regression methods were used to elucidate the nature of the radiation-associated risks per Gy of weighted absorbed colon dose using both excess relative risk (ERR) and excess absolute risk (EAR) models adjusted for smoking. Risk estimates were reported for a person exposed at age 30 years with attained age of 70 years. In this study, 22,538 incident first primary solid cancer cases were identified, of which 992 were associated with radiation exposure. There were 5,918 cases (26%) that occurred in the 11 years (1999–2009) since the previously reported study. For females, the dose response was consistent with linearity with an estimated ERR of 0.64 per Gy (95% CI: 0.52 to 0.77). For males, significant upward curvature over the full dose range as well as restricted dose ranges was observed and therefore, a linear-quadratic model was used, which resulted in an ERR of 0.20 (95% CI: 0.12 to 0.28) at 1 Gy and an ERR of 0.010 (95% CI: −0.0003 to 0.021) at 0.1 Gy. The shape of the ERR dose response was significantly different among males and females ($P = 0.02$). While there was a significant decrease in the ERR with increasing attained age, this decrease was more rapid in males compared to females. The lowest dose range that showed a statistically significant dose response using the sex-averaged, linear ERR model was 0–100 mGy ($P = 0.038$). In conclusion, this analysis demonstrates that solid cancer risks remain elevated more than 60 years after exposure. Sex-averaged upward curvature was observed in the dose response independent of adjustment for smoking. Findings from the current analysis regarding the dose-response shape were not fully consistent with those previously reported, raising unresolved questions. At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies. Upcoming results from a series of analyses focusing on the radiation risks for specific organs or organ families, as well as continued follow-up are needed to fully understand the nature of radiation-related cancer risk and its public health significance. Data and analysis scripts are available for download at: http://www.rerf.or.jp. **© 2017 by Radiation Research Society**

INTRODUCTION

The Life Span Study (LSS) of atomic bomb survivors in Hiroshima and Nagasaki, Japan, provides quantitative estimates of cancer risks associated with exposure to low-linear energy transfer (LET) radiation and is a major source of human data used for radiation risk assessment in establishing radiation safety standards. Long-term follow-up of this cohort continues to provide updated information on temporal patterns of radiation-related risk of cancer. Mortality follow-up data, based on Japan's nationwide system of recording deaths, have been reported 14 times since 1961, with the most recently reported data covering the follow-up period through 2003 (*1*). Mortality data, although highly valuable, do not provide adequate information on less fatal cancers. LSS cancer incidence data derived from linkage with local population-based cancer

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registries enable risk estimates for both fatal and nonfatal cancers with better diagnostic accuracy and disease onset date. Results of comprehensive analyses of solid and hematopoietic cancer incidence data among the LSS with follow-up through 1987 were first reported in 1994 (*2*, *3*) and updated for solid cancer incidence with follow-up through 1998 in 2007 (*4*). Incident hematopoietic cancer data were recently updated through 2001 (*5*).

The principal finding regarding solid cancer risks from the follow-up, both incidence and mortality, of this cohort has been a persistent increase in solid cancer risks due to radiation exposure that occurred at the time of the bombings in 1945. The radiation dose response for all solid cancers as a group was previously observed to be linear with no evidence of a threshold. The excess relative risk (ERR) per unit dose of radiation for all solid cancers has been found to decrease with increasing attained age while the excess absolute risks (EARs) have increased with attained age throughout the follow-up period (*4*).

This article covers the third comprehensive analysis of LSS solid cancer incidence risks, adding 11 years of follow-up to the previously reported study (*4*), extending the overall follow-up period to 52 years, i.e., up to 64 years after exposure. For this analysis, we have incorporated several significant improvements in the data and methods. Individual radiation dose estimates have been revised, as described by Cullings *et al*. (*6*). Briefly, the system for calculating the doses is largely unchanged from Dosimetry System 2002 (DS02) but the input parameters regarding a survivor's location and shielding information at the time of the bombing have been updated based on a thorough review of original materials. We updated estimates of migration rates that account for cohort members moving out of and returning to the cancer incidence catchment areas, re-appraised the appropriateness of cancers not clinically evident but identified only via the autopsy program for atomic bomb survivors and censored certain *in situ* cancers that had been counted in some earlier reported studies. We also prepared and made use of lifestyle data, specifically smoking data, obtained from various surveys of LSS cohort members.

This analysis concerns the radiation risks of all solid cancers in aggregate, focusing on the shape of the dose response after adjusting for age, sex, birth cohort and smoking. Radiation-risk modifiers included attained age, age at exposure and sex. Subsequent organ or system-specific reports will follow and provide detailed dose-response analyses that address various topics of interest while including relevant lifestyle risk factors.

MATERIALS AND METHODS

Life Span Study Cohort

The Life Span Study cohort of 120,321 subjects includes 93,741 atomic bomb survivors of Hiroshima and Nagasaki and 26,580 persons who were not in either city [''not in city'' (NIC)] at the time of the bombings. Details of the sampling methods are described elsewhere (*7*, *8*). Briefly, approximately 284,000 atomic bomb survivors were enumerated at the time of the 1950 National Census. Among them, roughly 190,000 who were still living in Hiroshima or Nagasaki at the time of the census served as the basis for selecting the 94,000 survivors in this cohort; the cohort consists of 54,000 persons who were within 2.5 km of the hypocenter and thus exposed to relatively high doses of radiation (i.e., proximal survivors) and 40,000 city, age and sex-matched survivors who were between 2.5 and 10 km of the hypocenter who were exposed to lower or negligible doses (i.e., distal survivors). The NIC subjects were identified by separate city censuses and frequency matched to the survivors on city, sex and age. The NIC group was included in the risk analyses to improve estimates of temporal and birth cohort patterns of background (baseline) cancer rates, as previously reported elsewhere (*4*).

Ascertainment of the vital status of LSS members was facilitated by the Japanese national family registry system (*koseki*), which is virtually complete. Since systematic solid cancer incidence ascertainment was not possible until the Hiroshima and Nagasaki population-based tumor registries were established in 1958, analyses of incidence data were limited to a subset of the LSS cohort members who were alive and not known to have had cancer prior to January 1, 1958. After excluding those who had died or been diagnosed with cancer prior to January 1, 1958 (n = 8,317), along with those who could not be traced using *koseki* (n = 86) and one person who was followed up in duplicate, the LSS solid cancer incidence cohort consisted of 111,917 (93% of the LSS cohort members). In the analysis, we also excluded 6,473 survivors for whom Dosimetry System 2002 Revision 1 (DSO2R1) doses (described later) could not be estimated. Thus, the total number of subjects considered in the current analysis was 105,444 (consisting of 80,205 survivors and 25,239 NIC subjects).

Table 1 shows distribution of the subjects in the LSS solid cancer incidence cohort by vital status and age at exposure by sex. As of the end of follow-up on December 31, 2009, 37.7% of members (33.6% of males and 40.5% of females) were alive. The majority (83.4%) of those alive at the end of follow-up were exposed as children (less than 10 years old). Among all those exposed at less than 20 years of age, 72.7% were alive at the end of follow-up while follow-up of those exposed after 30 years of age was virtually complete.

Ascertainment of Incident Cancer Cases

Cancer incidence follow-up of the LSS subjects is conducted using various data sources with linkage to Hiroshima and Nagasaki based city and prefecture-wide cancer incidence registry systems. Cancer registry data were supplemented by information from several RERF sources, including the Adult Health Study (AHS) and Atomic Bomb Casualty Commission/Radiation Effects Research Foundation (ABCC/RERF) surgical and autopsy programs. Members of the AHS cohort, a subset of the LSS cohort, have been invited to undergo biennial clinical health examinations since 1958. Under the ABCC/RERF autopsy program, extensive postmortem examinations were performed from 1948 to 1988, targeting LSS cohort members. The cancer registries were the principal sources of cancer incidence data (>86% of cases).

The focus of the current analysis was on first primary solid cancers diagnosed in the Hiroshima and Nagasaki cancer registry catchment areas between 1958 and 2009. We grouped solid cancers using ICD-O-3 topography codes C00–C89 with behavior code 3 (malignant), plus brain and central nervous system tumors of benign or uncertain/unknown behavior [ICD-O-3 topography codes C70–C72, pituitary gland code C751, craniopharyngeal duct code C752, and pineal gland code C753 with behavior code 0 (benign) or 1 (uncertain or unknown nature)]. We excluded leukemia, lymphoma, myeloma and other lymphohematopoietic malignancies (ICD-O-3 morphology codes 9590–9970). *In situ* cancers and intramucosal colorectal carcinomas were ignored. In addition, otherwise eligible cases with a diagnosis based solely on postmortem examination under the ABCC/RERF

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TABLE 1
Number and Percentage of Subjects Alive as of December 31, 2009 by Age at Exposure and Sex: LSS Solid Cancer Incidence Cohort, 1958–2009

Age at exposure (years)	Male			Female			Total		
	Subjects	Alive	Percentage	Subjects	Alive	Percentage	Subjects	Alive	Percentage
<10	11,633	9,020	77.6	11,929	10,615	89.0	23,562	19,644	83.4
10–19	11,194	5,647	50.4	14,248	10,323	72.5	25,442	15,970	62.8
20–29	3,685	618	16.8	11,677	5,048	43.3	15,352	5,666	36.9
30–39	5,714	96	1.7	10,928	747	6.8	16,642	843	5.1
40–49	7,419	6	0.1	9,458	9	0.1	16,877	15	0.1
≥50	6,219	0	0.0	7,832	0	0.0	14,042	0	0.0
All ages	45,864	15,369	33.6	66,053	26,742	40.5	111,917	42,138	37.7

autopsy program (''autopsy-only cases'') were not counted as cases and were censored at the time of death for reasons explained in Appendix A. We note that many of these cases were designated as ''occult'', and while they were excluded from the first published cancer incidence study (*2*), they were included in the most recently published study (*4*).

Radiation Doses (DS02R1)

Dosimetry System 2002 Revision 1 (DS02R1) was used to estimate individual organ doses received by LSS subjects exposed to radiation from the bombings. DS02R1 is an updated version of Dosimetry System 2002 (DS02), which has been fully described elsewhere (*6*). The primary changes from DS02 were updates to both location and terrain shielding data (i.e., dosimetry system input parameters) and other minor corrections. Location improvements were based on a thorough review of original questionnaire data pertaining to location at the time of the bombing (ATB) recorded from the survivors in the period of 1949–1963. Included in the corrections of systematic errors was the restoration of map coordinate digits that had previously been truncated due to limitations in early data storage methods. In addition, distortions discovered in the WWII-era maps used to identify the survivors' locations were corrected with digital mapping software. Corrections of other errors included simple transcription mistakes as well as incorrectly located survivors. In addition to the location improvements, terrain shielding was updated based on modern terrain data, resulting in a substantial increase in the number of persons determined to have shielding from the bomb due to land features, particularly in Nagasaki.

Weighted absorbed colon dose (Gy) was calculated as the sum of the gamma-ray dose plus ten times the neutron dose to allow for the greater biological effectiveness of neutrons. As in DS02, weighted absorbed colon doses for people with total shielded kerma doses greater than 4 Gy were truncated so that the total shielded kerma dose was 4 Gy, however, the method for apportioning the levels of truncation between gamma and neutron doses was changed, as previously documented by Cullings *et al*. (*6*). Briefly, the neutron-to-gamma ratio is very high for those with an estimated total shielded kerma greater than 4 Gy. This high ratio was reduced to the average ratio of survivors with an estimated total shielded kerma of 4 Gy. Interestingly, this method of adjustment was used in the early DS86 era when doses were truncated to 6 Gy (*6*). Table 2 shows the DS02R1 weighted absorbed colon dose distribution among the LSS solid cancer incidence cohort.

To reduce attenuation biases due to dose errors, unadjusted dose estimates were replaced with expected survivor dose estimates (*9*) assuming 35% coefficient of variation in errors for individual doses. This method of dose error adjustment is not affected by the corrections in location, shielding or map distortions described above. DS02R1 included doses calculated for 15 organ sites. The current analyses for solid cancer used DS02R1 colon dose, which served as a representative dose for all organs. All organ doses are highly correlated, meaning this arbitrary choice has little influence on overall radiation risk inferences. Those with unknown doses, due to unknown or complex shielding conditions that precluded estimation, were excluded from the analyses.

Smoking Data

Smoking data were ascertained from four LSS mail surveys and three AHS clinic-based questionnaires administered between 1963 and 1991 (*10–14*), as described by Furukawa *et al*. (*15*). Among the 105,444 LSS cohort members used in these analyses, 63,040 (60%) provided information on smoking habits on at least one questionnaire prior to their initial cancer diagnosis or end of follow-up. We summarized the smoking history with indicators of last known smoking status (never, past, current and unknown) and, for those with a smoking history, starting age, average intensity and last age at which they were known to have smoked.

Organization of the Data for Analyses and Statistical Methods

The analyses were based on a highly stratified table of person-time and numbers of cases by city (Hiroshima or Nagasaki), sex (male or female), age at exposure (14 five-year categories from 0 to 69 and one of ≥70), attained age (15 five-year categories from 10 to 84 and one of ≥85–<110), time period of cancer diagnosis [13 categories: 1958–1960, 1961–1965, 1966–1970, 1971–1975, 1976–1980, 1981–1985, 1986–1987, 1988–1990, 1991–1995, 1996–1998 (cutoff for the previously reported study), 1999–2000, 2001–2004 and 2005–2009], NIC status (>10,000 m from the hypocenter), DS02R1 weighted absorbed colon dose (22 categories with dose cutoff points at 0, 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5 and 3 Gy) and an indicator of high dose (unweighted gamma plus neutron shielded kerma >4 Gy).

Further time-dependent stratification was also performed for smoking. Smoking history was considered unknown for all cohort members prior to the time they first provided smoking history information. Individual smoking histories were considered as known thereafter. In addition to smoking status categories, the smoking data were stratified by average cigarettes per day (seven categories with cutoff points at 0, >0, 7.5, 12.5, 17.5, 22.5, 27.5), duration (6 categories with cutoff points at 0, >0, 5, 10, 20 and 30 years) and years since quitting (5 categories with cutoff points at 0, >0, 5, 10 and 15). Approximately 40% of the person-years and 60% of the cases in these analyses were accumulated after ascertainment of smoking status. For those with smoking history information, smoking status (never, current or past smoker) was considered to remain unchanged from the latest survey on which they provided information until the end of follow-up. Males who did not provide smoking information were analyzed in an ''unknown'' category while females who did not

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TABLE 2
Distribution of Weighted Absorbed Colon Dose by Sex, City and Age at Exposure: LSS Solid Cancer Incidence Cohort, 1958–2009

	Eligible LSS members[a]	Subjects with known dose (%)	No. of subjects (%) per DS02R1 colon dose indicated					Dose unknown
			NIC	0–0.005 Gy	0.005–0.5 Gy	0.5–1 Gy	≥1 Gy	
Sex								
Male	45,864	42,910 (100)	10,488 (24)	14,574 (34)	15,608 (36)	1,282 (3)	958 (2)	2,954
Female	66,053	62,534 (100)	14,751 (24)	21,404 (34)	23,423 (37)	1,854 (3)	1,102 (2)	3,519
City								
Hiroshima	76,549	73,401 (100)	19,249 (26)	20,087 (27)	30,556 (42)	2,100 (3)	1,409 (2)	3,148
Nagasaki	35,368	32,043 (100)	5,990 (19)	15,891 (50)	8,475 (26)	1,036 (3)	651 (2)	3,325
Age at exposure (years)								
<10	23,562	22,708 (100)	4,995 (22)	7,928 (35)	8,909 (39)	505 (2)	371 (2)	854
10–19	25,442	23,079 (100)	5,878 (25)	7,973 (35)	7,750 (34)	892 (4)	586 (3)	2,363
20–29	15,352	14,251 (100)	3,675 (26)	4,718 (33)	5,070 (36)	478 (3)	310 (2)	1,101
30–39	16,642	15,838 (100)	4,034 (25)	5,127 (32)	5,953 (38)	418 (3)	306 (2)	804
40–49	16,877	16,074 (100)	3,727 (23)	5,472 (34)	6,067 (38)	504 (3)	304 (2)	803
≥50	14,042	13,494 (100)	2,930 (22)	4,760 (35)	5,282 (39)	339 (3)	183 (1)	548
Total	111,917	105,444 (100)	25,239 (24)	35,978 (34)	39,031 (37)	3,136 (3)	2,060 (2)	6,473

Note. NIC = not in either city.
[a] Alive and not known to have cancer as of the start of follow-up.

provide information were considered nonsmokers due to the high prevalence of smoking among males and the low prevalence of smoking among females. Almost 70% of the person-years for people with known smoking status were accumulated after the last date at which their smoking status was known. Total pack-years of smoking at the time of the first questionnaire were calculated from the intensity and number of years reportedly smoked. Pack-years accrued with additional years of smoking after the time of the first questionnaire.

Person-years of observation were computed from January 1, 1958 until the earliest date of diagnosis of any cancer (including hematopoietic cancers and cancers diagnosed outside of the catchment area, but excluding *in situ* and intramucosal colorectal carcinomas), date at which the subject reached 110 years of age, date of death or December 31, 2009, whichever occurred first. Since cancers that were diagnosed outside of the catchment areas could generally not be detected, person-years were adjusted for migration into and out of the catchment areas, as discussed in Appendix B.

Risk Models

Regression models to describe cancer risks included a description of the rates for unexposed (zero dose) nonsmokers (baseline rate) with additional terms for radiation and smoking effects. We described the joint effects of radiation and smoking in various ways, including additive and multiplicative ERR models and additive excess rate models (EAR). Ignoring smoking, the ERR model was:

$$BKG_{ALL}(1 + ERR_{rad}),$$

where BKG_{ALL} represents baseline rates for those not exposed to radiation (i.e., unexposed), and ERR_{rad} was the excess relative risk for radiation exposure.

The multiplicative ERR model for the joint effect of radiation and smoking was:

$$BKG_{NS}(1 + ERR_{smk})(1 + ERR_{rad}),$$

in which BKG_{NS} was the baseline rate for unexposed nonsmokers, ERR_{smk} was the excess relative risk for smoking, and ERR_{rad} was the excess relative risk for radiation. In this model, ERR_{rad} described the radiation-associated proportional increase in rates relative to unexposed people with the same smoking history. If smoking was not an effect modifier (that is, ERR_{rad} did not depend on smoking history), this increase was independent of smoking history.

The additive ERR model of the joint effect of radiation and smoking was:

$$BKG_{NS}(1 + ERR_{smk} + ERR_{rad}).$$

In this model, ERR_{rad} describes the radiation-associated proportional increase in rates relative to the risk for unexposed, nonsmokers.

An additive excess rate (or EAR) model for the joint effect of radiation and smoking on cancer rates was:

$$BKG_{NS} + EAR_{smk} + EAR_{rad},$$

where EAR_{smk} and EAR_{rad} described the smoking and radiation effects in terms of rate differences.

What follows are details of the model forms used for the baseline, ERR and EAR terms considered in these analyses.

Unexposed Nonsmoker (Baseline) Rates

Logarithms of the cancer rates for unexposed nonsmokers were modeled as sex-specific quadratic splines in log-attained age with sex-specific log-linear trends in year of birth (i.e., age at exposure). The baseline rate model included city-specific effects for the NIC group. A main effect for city was considered but not included in the final model, since it was not significant ($P > 0.05$). The background function was parameterized as:

$$exp\left\{\alpha_s + \gamma_s \log\left(\frac{a}{70}\right) + \epsilon_s log^2\left(\frac{a}{70}\right) + [\eta_s log^2\left(\frac{a}{70}\right)]_{a>70} + \theta\left(\frac{byr - 1915}{10}\right) + city * NIC\right\},$$

where all ''*s*'' subscripts indicate sex-specific parameters, *a* is age in years, *byr* is birth year and *NIC* is a ''not in city'' indicator.

Radiation Effect Models

The radiation ERR and EAR were described using models of the form $\rho(d, s)\,\varepsilon(s, a, e, x)$, in which $\rho(d, s)$ is a function of dose (d) describing the possibly sex-dependent shape of the dose response and $\varepsilon(s, a, e, x)$ is a function describing effect modification as a function of sex (s), attained age (a), age at exposure (e) and other variables (x)

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discussed in greater detail below. The following dose-response models were considered:

Linear: $\rho(d, s) = \beta_s d$

Linear quadratic (more below): $\rho(d, s) = \beta_{1s} d + \beta_{2s} d^2$

Linear threshold: $\rho(d, s) = \left\{ \begin{array}{cc} \beta_s(d - D_1) & d > D_1 \\ 0 & d \le D_1 \end{array} \right\}$

"Nonparametric": $\rho(d, s) = \sum \theta_{is} I(D_i \le d < D_{i+1})$.

The sex-dependent linear-quadratic (LQ) dose-response model could be rewritten as $\beta_{1s}(d + \sigma_s d^2)$, where $\sigma_s = \beta_{2s}/\beta_{1s}$ (if $\beta_{1s} \neq 0$) and was a measure of the curvature in the dose response. Linear-quadratic models in which the linear slope could depend on sex but the curvature was independent of sex were also considered. This common curvature model was $\beta_{1s}(d + \sigma d^2)$. For some analyses, focus was placed on the nature of the dose response over the limited dose range from 0 to D_{lim}, where D_{lim} was the dose of interest. 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 $\beta_{1s} d_{lo} + \beta_{2s} d_{lo}^2 + \beta_{3s} d_{hi} + \beta_{4s} d_{hi}^2$ or reparameterized to provide estimates of the curvature parameter(s). The primary concern was the values of the parameters over the low-dose range (i.e., β_{1s}, β_{2s}); effect modifiers were common to the full-dose range.

In some plots showing categorical dose-response estimates, the ERR estimates, plotting positions and confidence limits were smoothed using running weighted-average smoothers. The weights for these smoothers were defined as the product of fixed smoothing weights and the inverses of the standard errors of the category-specific risk estimates. Three-point smoothing was used for the lowest and highest categories while five-point smoothing was used for all other dose categories. These values were then smoothed using a locally weighted regression smoother (Lowess) (*16*) with a bandwidth of 0.25 (see Appendix E). The dose categories used for the 22 nonparametric categorical risk estimates are provided above (Organization of the Data for Analyses and Statistical Methods section).

Effect modification of the ERR or EAR [i.e., $\varepsilon(s, a, e, x)$, from above] was described using log-linear models with the basic form $exp\{\delta_1 \log(\frac{a}{70}) + \delta_2(\frac{e-30}{10}) + \phi I(K>4)\}$, where attained age and age at exposure were scaled so they corresponded to attained age 70 after exposure at age 30. The last term in this model was an adjustment intended to limit the impact of survivors with total shielded kerma estimates (K) more than 4 Gy. As in most recent LSS analyses, this adjustment was included because it was believed such survivor doses were erroneously high but were included to bolster the power of the effect modifiers. In some analyses the effect modifiers could include sex-dependent effects. Effect modification by time-since-exposure and age-at-exposure was also considered [replacing the $\delta_1 \log(\frac{a}{70})$ term with $\delta_1(\frac{years\ since\ exposure - 40}{10})$ in the preceding equation], but are only briefly reported.

Smoking Effect Models

The ERR for smoking (ERR_{smk}) was modeled as linear in time-dependent pack years (a measure of cumulative number of cigarettes smoked) with allowance for additional log-linear dependence on the log of smoking intensity and log duration. This model was chosen for its similarity to a model previously described by Furukawa *et al.* (*15*). Model values were scaled so that the reported smoking ERR estimates corresponded to the risk for a continuing 70-year-old one-pack-per-day smoker who started smoking at age 20. This model implied that the smoking ERR was proportional to the product of intensity to a power and duration to a (possibly different) power. If a person stopped smoking, duration was fixed at its value at their reported age at smoking cessation. The smoking effect model allowed for changes in the post-smoking ERR through the inclusion of a function of the logarithm of 1 plus years since quitting. Letting *cpd* represent smoking intensity in cigarettes per day, *smkdur* be the (time-dependent) duration of smoking in years, *tsq* be the (time-dependent) number of years after smoking cessation, and *packyrs* be the total time-dependent number of pack years, the basic form of ERR_{smk} was:

$$ERR_{smk} = \beta_s \left(\frac{packyrs}{50}\right) e^{\theta_1 \log\left(\frac{cpd}{20}\right) + \theta_2 \log\left(\frac{smkdur}{50}\right) + \theta_3 \log(1+tsq),}$$

$$\text{given: } packyrs = smkdur * \frac{cpd}{20},$$

$$ERR_{smk} = \beta_s \left(\frac{cpd}{20}\right)^{1+\theta_1} \left(\frac{smkdur}{50}\right)^{1+\theta_2} (1 + tsq)^{\theta_3}$$

Sex effects on the smoking ERR (β_s) were also considered, as well as models that allowed for modification of the smoking effect by sex-dependent functions of attained age and birth cohort. The smoking intensity, duration and time-since-quitting effects on the smoking excess rate (EAR_{smk}) were described using a model with the same form as that for ERR_{smk} given above with additional sex-specific effect modification by attained age and birth cohort. The smoking effect models also included sex-dependent effects for people with unknown smoking status.

Radiation risks were reported per Gy (or Gy^2 for quadratic terms) of weighted absorbed colon dose. Estimated parameters, likelihood ratio tests, likelihood-based 95% confidence intervals and Wald-based 95% confidence intervals (for estimates of combined linear and quadratic terms) were computed with the AMFIT computer program from the Epicure risk regression software (*17*).

Ethical Considerations and Data Access

This study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation (RP 1-75: Research plan for RERF study of Life-span of A-bomb survivors, Hiroshima and Nagasaki; RP 18-61: Tumor registry study in Hiroshima and Nagasaki). The Hiroshima and Nagasaki Prefectures and the city of Hiroshima approved the linkages between LSS cohort members and data from the Cancer Registries. Data and analysis scripts are available for download at: http://www.rerf.or.jp.

RESULTS

Characteristics of all Solid Cancer Cases and Crude Incidence Rates

During the study period from 1958 until the end of 2009, a total of 24,448 first primary cancers were diagnosed within the catchment areas among the 105,444 subjects in the final analysis cohort. After excluding hematopoietic cancers (n = 1,290) and cancers diagnosed only at autopsy (n = 620), 22,538 solid cancers remained for analysis. Among these eligible cases, 5,918 cases (26%) occurred in the 11 years (1999–2009) since the end of the follow-up period for the previous LSS solid cancer incidence analysis (*4*).

The stomach was the most common cancer site for both males and females and accounted for 29.5% of cases among males and for 21.3% among females. Other commonly occurring cancer sites included the lung (13.8%), liver (10.7%), colon (7.5%) and rectum (4.9%) among males, and breast (12.2%), colon (9.4%), lung (8.3%) and cervix uteri (7.3%) among females (see appendix table C1). For 76.7%

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TABLE 3
Number of Subjects, Solid Cancer Cases, Person-Years of Follow-up and Crude Incidence Rate by Sex, City, Age at Exposure, Attained Age and DS02R1 Weighted Colon Dose: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

	Both sexes				Males				Females			
	No. of subjects	Person-years	No. of cases	Rate per 10^4	No. of subjects	Person-years	No. of cases	Rate per 10^4	No. of subjects	Person-years	No. of cases	Rate per 10^4
City												
Hiroshima	73,401	2,193,282	16,387	74.7	29,498	807,723	7,566	93.7	43,903	1,385,559	8,821	63.7
Nagasaki	32,043	886,203	6,151	69.4	13,412	334,477	2,907	86.9	18,631	551,726	3,244	58.8
Age at exposure (years)												
0–19	45,787	1,629,029	8,690	53.3	21,588	727,781	4,845	66.6	24,199	901,249	3,845	42.7
20–39	30,089	988,517	8,463	85.6	8,525	238,547	2,909	121.9	21,564	749,970	5,554	74.0
40–	29,568	461,938	5,385	116.6	12,797	175,872	2,719	154.6	16,771	286,066	2,666	93.2
Attained age (years)												
<40	56,657	646,102	450	7.0	23792	292,684	128	4.4	32,865	353,417	322	9.1
40–	15,260	486,309	1,178	24.2	4,889	187,441	402	21.4	10,371	298,868	776	26.0
50–	16,637	614,709	3,210	52.2	6,796	229,557	1,477	64.3	9,841	385,152	1,733	45.0
60–	11,258	651,170	6,491	99.7	5,228	238,159	3,504	147.1	6,030	413,010	2,987	72.3
70–	4,649	457,149	6,990	152.9	1,874	143,814	3,428	238.4	2,775	313,335	3,562	113.7
80–	983	224,046	4,219	188.3	331	50,545	1,534	303.5	652	173,501	2,685	154.8
DS02R1 weighted colon dose (Gy)												
NIC	25,239	761,569	5,222	68.6	10,488	287,800	2,560	89.0	14,751	473,769	2,662	56.2
<0.005	35,978	1,032,561	7,370	71.4	14,574	378,725	3,452	91.1	21,404	653,836	3,918	59.9
–0.1	27,511	807,885	5,674	70.2	11,175	302,141	2,635	87.2	16,336	505,744	3,039	60.1
–0.2	5,594	164,111	1,217	74.2	2,132	57,898	497	85.8	3,462	106,213	720	67.8
–0.5	5,926	169,177	1,414	83.6	2,301	59,840	599	100.1	3,625	109,337	815	74.5
–1	3,136	88,992	889	99.9	1,282	32,202	382	118.6	1,854	56,790	507	89.3
–2	1,565	42,236	560	132.6	716	17,815	254	142.6	849	24,420	306	125.3
2+	495	12,953	192	148.2	242	5,778	94	162.7	253	7,175	98	136.6
Total	105,444	3,079,484	22,538	73.2	42,910	1,142,200	10,473	91.7	62,534	1,937,284	12,065	62.3

Note. NIC = not in either city.

of the cases, cancer diagnosis was verified histologically (85% of cases since 1999). The percentage of histologically confirmed cases was 90% or higher for cancers of the oral cavity, rectum, skin (nonmelanocytic), breast, uterine cervix, uterine corpus, prostate and thyroid. Liver cancer cases had the lowest percentage of histologically confirmed diagnosis (38.6%). For 9.2% of the cases, cancer diagnosis was made via the death certificate only (DCO) and not confirmed elsewhere (see appendix table C2).

Approximately 70% of the LSS cohort were residents of Hiroshima and slightly more than half (59%) were females (Table 3); 251 persons had estimated shielded kerma >4 Gy. The crude solid cancer incidence rate in Hiroshima (74.7/10^4 person-years) was higher than that in Nagasaki (69.4/10^4 person-years). The rates for males were higher than those for females in both cities, and the rate ratios (male to female) were the same in both cities (1.47). The mean age at diagnosis for all solid cancers was 68.6 years old. Rates among subjects less than 40 years of age were higher in females than in males; rates among subjects over the age of 40 were higher among males than females.

Baseline Cancer Rates (Nonsmoker with no Radiation Exposure)

We developed a multiplicative model to quantify cancer risks for radiation exposure status while adjusting for smoking status. While estimates were derived simultaneously, we present the aspects of the model sequentially: first, a description of the baseline cancer rates, then the cancer risks in relationship to smoking, and finally, the radiation risks of cancer adjusted for smoking.

Figure 1 shows the fitted nonsmoker baseline rates for males and females (Fig. 1A), and the sex ratio of baseline rates (Fig. 1B) for three birth cohorts (1895, 1915 and 1935) as a function of attained age.

Baseline solid cancer rates increased roughly in proportion to the fifth power of attained age in males and to the third power in females. This increase lessened somewhat at older ages, especially among males. As a result, the age-specific female-to-male (F:M) cancer rate ratio decreased from approximately three at age 30 to one at around age 50, falling below one at older ages. When sex-specific cancers were excluded, the F:M cancer rate ratios were consistently below one in adulthood (not shown). This suggests that the higher incidence rates seen in younger females were largely a reflection of sex-specific cancer incidence in this population. Cancer incidence rates increased by approximately 15% for males and 6.5% for females per decade increase in birth year, regardless of attained age, resulting in the lower F:M ratio seen in later birth cohorts. As follow-up began 13 years after the bombings, a total of 8 cancers were observed prior to age 20 (four each among males and

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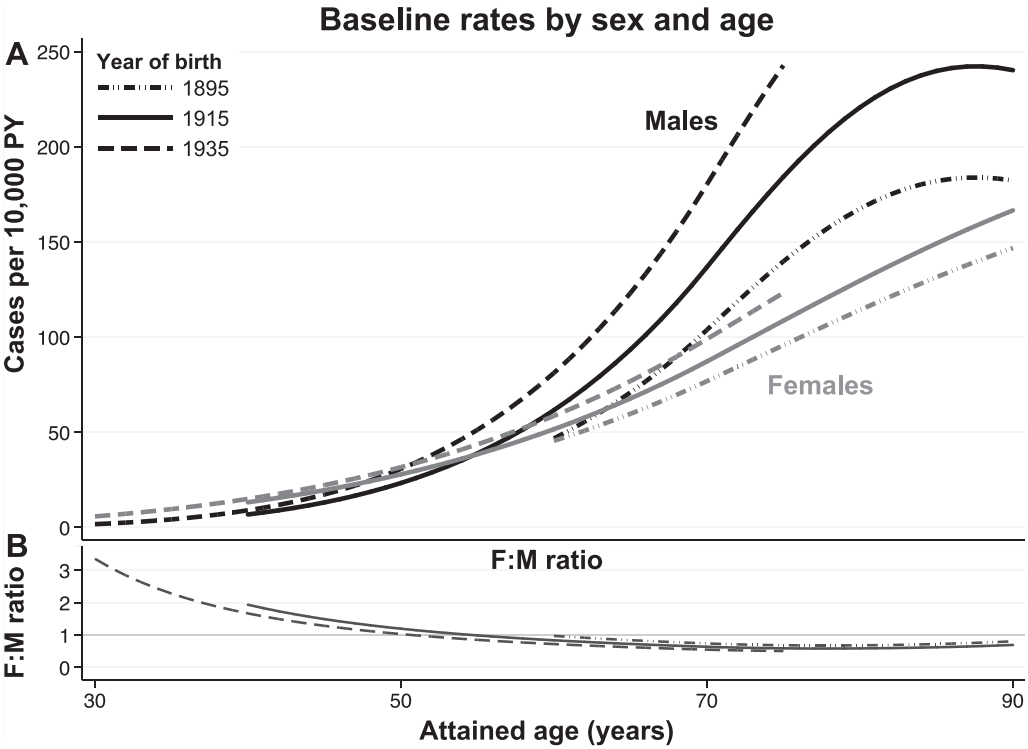


FIG. 1. Solid cancer baseline rates. Panel A: Fitted Life Span Study all-solid-cancer incidence rates for nonsmokers with no exposure (baseline rates) for the period from 1958 to 2009 versus attained age and by sex for three birth years (1895, 1915 and 1935) and averaged across cities based on a multiplicative model that included radiation and smoking. Panel B shows how the female-to-male sex ratio (F:M) varied with attained age for these three birth cohorts.

females) and an additional 57 cases were observed between ages 20 and 30 (18 among males and 39 among females). In total, 99.7% of all observed cancers occurred after age 30.

Baseline (Smoker) Cancer Rates and Smoking Effect Estimates

Roughly 60% of the LSS subjects provided smoking information. Of those, 85% of males and approximately 20% of females were identified as ever-smokers (Table 4). There was no appreciable variability in the proportion of ever-smokers with distance or dose categories in either city. The NIC were generally not included in the mail surveys, which accounts for their markedly lower proportion of subjects with ''known smoking status.'' Note that city-specific NIC terms were included in the model to allow for variations in background cancer rates.

For male smokers, mean age at the start of smoking was 21.5, while females typically started approximately 11 years later (mean 32.3). Starting age for males was less variable (standard deviation 5.4) than for females (standard deviation 11.2). Male smokers reported smoking more cigarettes per day [mean 19 cigarettes per day (cpd)] than female smokers (mean 10 cpd). As of the most recent survey, 29% of male ever-smokers and 33% of female ever-smokers indicated that they had stopped smoking, with males stopping at slightly lower ages (mean 51.9) than females (mean 56.8).

In the basic model for ERR_{smk}, there was a highly significant effect of smoking on the risk of all solid cancers with an estimated ERR_{smk} of 0.75 (95% CI 0.65 to 0.84) for a pack-a-day smoker who had smoked for 50 years and started at age 20, with a nonlinear dependence on both smoking duration and intensity. The smoking ERR increase was significantly sublinear for smoking intensity and supralinear for smoking duration. The ERR_{smk} for a 50-pack-year smoker decreased with intensity with the power of intensity to –0.55 ($P < 0.001$, 95% CI: −0.67 to −0.42) and increased with duration to the power of 0.46 ($P = 0.002$, 95% CI: 0.16 to 0.82). When the model was modified to allow ERR for past smokers to change with time since quitting, the ERR changed in proportion to years-since-quitting +1 to the power of −0.07. This slow decline was not significant ($P = 0.13$) and was therefore not used in the final ERR_{smk} model. There was no evidence of a simple sex-effect on ERR_{smk} ($P = 0.21$). Allowing for modification of the smoking effect by sex-dependent functions of attained age and birth cohort improved the overall fit of the model, but did not have any appreciable impact on inference of the radiation dose response, and were therefore not included in later models. Also, since the unknown smoking effect for females was not statistically significant from nonsmokers ($P > 0.50$), it was not included in the final ERR or EAR smoking models. This is not unexpected, since most women were nonsmokers. Counts of estimated cases attributable to

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TABLE 4
Smoking Status Data by Exposure Category: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

DS02R1 weighted colon dose category	Ever-smoker		Nonsmoker		Unknown		
	No.	(%)	No.	(%)	No.	(%)	Total (%)
			Males				
NIC	3,493	(33.3)	454	(4.3)	6,541	(62.4)	10,488 (100)
<0.005 Gy	7,830	(53.8)	1,365	(9.4)	5,369	(36.8)	14,574 (100)
–0.1 Gy	6,257	(56.0)	1,083	(9.7)	3,835	(34.3)	11,175 (100)
–0.2 Gy	1,242	(58.2)	213	(10.0)	677	(31.8)	2,132 (100)
–0.5 Gy	1,326	(57.6)	243	(10.6)	732	(31.8)	2,301 (100)
–1 Gy	753	(58.7)	127	(9.9)	402	(31.4)	1,282 (100)
–2 Gy	452	(63.1)	62	(8.7)	202	(28.2)	716 (100)
2+ Gy	145	(59.9)	26	(10.7)	71	(29.3)	242 (100)
Total	21,508	(50.1)	3,573	(8.3)	17,829	(41.6)	42,910 (100)
			Females				
NIC	1,065	(7.2)	5,578	(37.8)	8,108	(55.0)	14,751 (100)
<0.005 Gy	2,173	(10.2)	11,144	(52.1)	8,087	(37.8)	21,404 (100)
–0.1 Gy	2,009	(12.3)	8,814	(54.0)	5,513	(33.8)	16,336 (100)
–0.2 Gy	501	(14.5)	1,891	(54.6)	1,070	(30.9)	3,462 (100)
–0.5 Gy	540	(14.9)	2,014	(55.6)	1,071	(29.5)	3,625 (100)
–1 Gy	282	(15.2)	1,115	(60.1)	457	(24.6)	1,854 (100)
–2 Gy	159	(18.7)	489	(57.6)	201	(23.8)	849 (100)
2+ Gy	38	(15.0)	147	(58.1)	68	(26.9)	253 (100)
Total	6,767	(10.8)	31,192	(49.9)	24,575	(39.3)	62,534 (100)

Note. NIC = not in either city.

smoking and radiation using various models are shown in Appendix D.

Figure 2A shows how the ERR_{smk} varied with attained age for a typical lifelong male smoker (20 cigarettes per day from age 20) and a typical lifelong female smoker (10 cigarettes per day from age 30). The plot also indicates how the smoking ERR was affected by smoking cessation at age 50 for males and 55 for females, as indicated by the dashed lines. Figure 2B shows the total solid cancer rates for males and females with the above smoking histories, as well as baseline rates for nonsmokers (never smokers).

An analysis was performed to examine the extent to which the smoking effect on all solid cancer risk reflected the effects of smoking on known smoking-associated cancers (i.e., cancers of the oral cavity, larynx, lung, other respiratory, esophagus, stomach, pancreas, liver, kidney,

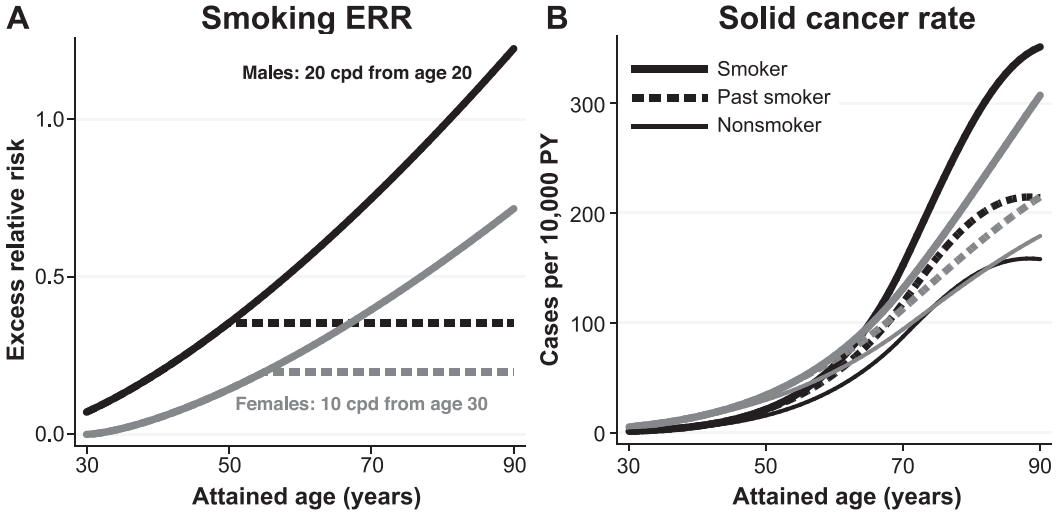


FIG. 2. Smoking effects on solid cancer baseline rates. Panel A: Smoking ERR as a function of attained age for males (black curves) and females (gray curves). The solid curves represent lifelong smokers while the dashed curves represent past smokers from the age at which they quit (shown are male past smokers quitting at age 50 years and female past smokers quitting at age 55 years). Panel B: Total smoking risk for current smokers, past smokers and those who never smoked (thin solid curves) for males and females. The curves represent typical smoking histories. Male smokers started at age 20 years and smoked 20 cigarettes per day while female smokers started at 30 years and smoked 10 cigarettes per day (cpd).

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TABLE 5
All Solid Cancer Linear ERR per Gy Adjusted for Modifying Effects of Age at Exposure and Attained Age with or without Adjustment for Smoking: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

ERR per Gy[a]					
Sex-averaged (95% CI)	Males (95% CI)	Females (95% CI)	F:M ratio (95% CI)	Age at exposure[b] (percentage change per 10-year increase) (95% CI)	Attained age[c] (power) (95% CI)
Unadjusted for smoking (deviation = 57,404.131, 17 parameters)					
0.50 (0.42 to 0.59)	0.36 (0.28 to 0.45)	0.65 (0.53 to 0.77)	1.80 (1.42 to 2.33)	–19% (–27% to –12%)	–1.57 (–2.01 to –1.11)
Adjusted for smoking, additive joint effect (deviation = 56,950.969, 21 parameters)					
0.56 (0.46 to 0.66)	0.48 (0.36 to 0.61)	0.64 (0.52 to 0.76)	1.33 (1.04 to 1.74)	–21% (–29% to –13%)	–1.53 (–1.98 to –1.07)
Adjusted for smoking, multiplicative joint effect (deviation = 56,959.086, 21 parameters)					
0.47 (0.39 to 0.55)	0.33 (0.25 to 0.42)	0.60 (0.49 to 0.72)	1.81 (1.42 to 2.35)	–21% (–29% to –12%)	–1.66 (–2.11 to –1.20)

[a] Estimates were centered and scaled to correspond with an attained age of 70 years after exposure at age 30 years.
[b] The age-at-exposure effect was expressed as percentage change per decade increase (e.g., in the top row, the per decade decrease is calculated as: $-19\% = 100*(\exp[-0.21*(\text{age exp} - 30) / 10] - 1)$, where -0.21 is the model parameter estimate and age_{exp} is age 40).
[c] The effect of attained age was modeled as power of attained age (e.g., in the top row: $[\text{age}_{\text{attained}}/70]^{-1.57}$)

bladder and other urinary and rectum), as defined by Doll *et al.* (*18*) The ERR_{smk} for smoking-related cancers among 70-year-old, pack-a-day smokers who smoked for 50 years was 1.27 (95% CI: 1.12 to 1.44), while the ERR_{smk} for nonsmoking-related cancers was 0.05 and not statistically significant.

Radiation Effects

ERR models. There was evidence of a statistically significant all-solid-cancer dose response in a linear ERR model without adjustment for smoking (Table 5, top panel) like that used in the previously reported solid cancer incidence study (*4*). In this model, the sex-averaged ERR for all solid cancers at attained age of 70 after exposure at age 30 was 0.50 per Gy (95% CI: 0.42 to 0.59), with the F:M ratio of 1.80 (95% CI: 1.42 to 2.33). The ERR varied significantly with both attained age ($P < 0.001$) and age at exposure ($P < 0.001$). Note that these values are quite similar to those previously reported, in which the sex-averaged ERR per Gy was estimated at 0.47 with a F:M ratio of 1.6; the modifying effect of attained age on the ERR was a decrease with age to the power of –1.65 while the ERR decreased by −17% per decade increase of age at exposure (*4*). When modifications by attained age and age at exposure were assessed separately and independently, their effects were somewhat larger with the current data; i.e., –2.02 for attained age and –28.6% for age at exposure. The lowest dose range that showed a statistically significant dose response using the sex-averaged linear ERR model with no adjustment for smoking (i.e., as in the top row of Table 5) was 0–100 mGy with an ERR estimate of 0.49/Gy (95% CI: 0.026 to 1.01; $P = 0.038$).

Smoking-adjusted radiation dose-response models. Smoking-adjusted linear ERR models, assuming either additive or multiplicative joint effects with radiation, fit the data markedly better than the unadjusted models (Table 5, middle and bottom rows). Due to the difference in sex-specific smoking prevalence, smoking-adjusted models primarily affected the radiation risk estimates for males and therefore, the ERR_{rad} sex-ratios, but there was little impact on the modification of the ERR per Gy estimates by attained age or age at exposure. ERR estimates were somewhat higher for the additive joint effect model than for the multiplicative joint effect model, especially for males. The reason for this is that in the additive model, the radiation-associated ERR was relative to the rate for nonsmokers, while in the multiplicative joint effect model, the radiation effect was measured relative to the risk for people with comparable smoking histories. Although an additive ERR model for the joint effect of radiation and smoking fit the data better than a multiplicative joint effect model, we used, unless explicitly noted, the results from the multiplicative joint effects model for the rest of the analyses. This decision was made for comparability to previously reported studies that ignored smoking, which results in radiation risk estimates relative to persons with the same smoking history (i.e., analogous to our current multiplicative joint effects model). This choice has almost no effect on inference regarding the dose-response shape or age-related effect modifiers, and helps to facilitate comparisons with the previous LSS results, as well as studies of other irradiated populations that did not adjust for smoking effects.

Age-at-Exposure Effects

Using the standard log-linear age-at-exposure model with attained-age effect modification and multiplicative adjustment for smoking, the linear ERR was estimated to decrease by 21% (95% CI: 12% to 29%) per decade increase in age at exposure. No model improvement was found when effect modification by age at exposure could vary by sex ($P > 0.5$) or city ($P > 0.5$). The BEIR VII model (*19*), which allowed for the ERR at 1 Gy to decrease with increasing age

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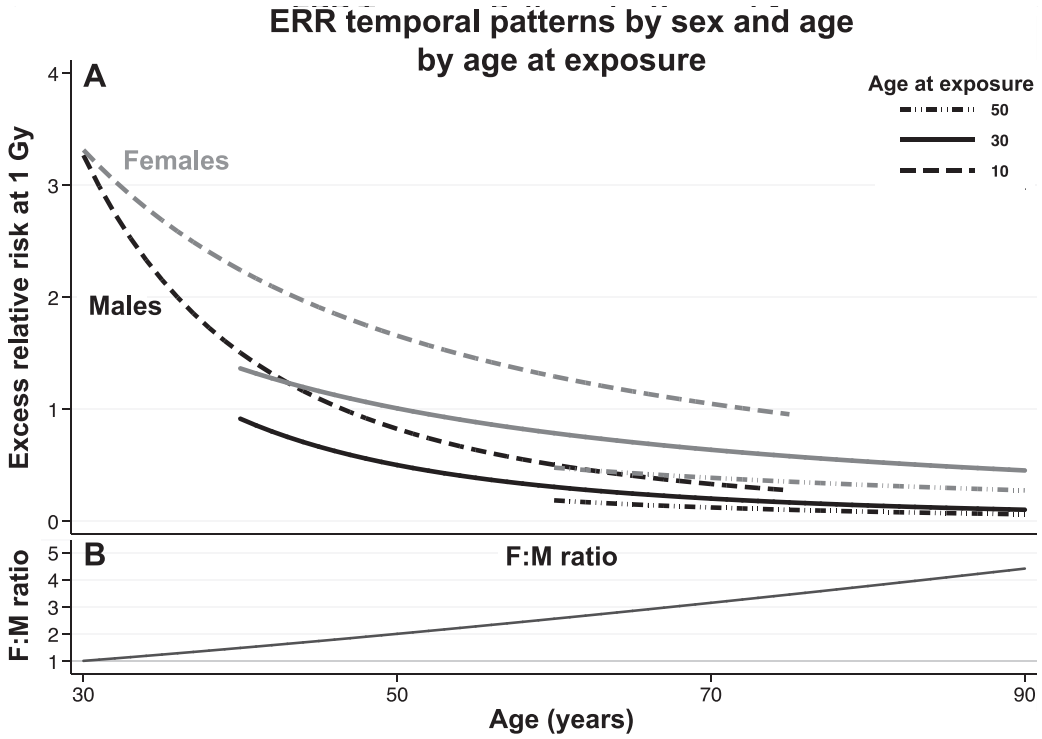


FIG. 3. Age-at-exposure and attained-age effects on solid cancer ERRs at 1 Gy by age at exposure and sex. Panel A shows how the radiation ERRs varied with attained age by sex (gray for females and black for males) and by age of exposure. This is a linear ERR model with multiplicative adjustment for smoking, sex-averaged age-at-exposure modification and sex-specific attained-age modification. Panel B shows how the female-to-male (F:M) ERR ratio varies with attained age at 1 Gy.

at exposure up to 30 years while remaining constant thereafter, did not fit the data significantly better than a simple log-linear age-at-exposure model ($P = 0.18$). Additional details on the age-at-exposure effect and how it is affected by inclusion of autopsy-only cases are given in Appendix A.

Attained-Age Effects

As previously found with both the solid cancer incidence (*4*) and mortality (*1*) data, the radiation ERR decreased significantly with attained age even after allowing for effect modification by age at exposure. In the basic analysis of the current data, the decrease in the radiation ERR with attained age was estimated to be proportional to age to the power of –1.66 (smoking-adjusted multiplicative ERR model in Table 5). When the model was extended to allow the attained-age effect to differ for males and females, there was a significant improvement in fit ($P = 0.016$), with the estimated decrease in radiation ERR more rapid for males than for females. Figure 3A plots the sex-specific estimated radiation ERR at 1 Gy as a function of attained age for three ages at exposure. The decrease in radiation ERR was proportional to attained age to the power of –2.56 (95% CI: –3.41 to –1.71) for males and –1.38 (95% CI: –1.88 to –0.86) for females. Figure 3B indicates how the female-to-male ERR ratio varies with attained age at 1 Gy.

Time-since-Exposure Effects

The three time scales (attained age, age at exposure and time since exposure) cannot be simultaneously modeled, since they are colinear. We tested a model with time since exposure and age at exposure. The radiation ERR decreased significantly with both time since exposure (27% per decade; $P = 0.001$) and age at exposure (43% per decade; $P = 0.001$). The Akaike information criterion (AIC) for this model was higher than that of a similar model with age at exposure and attained age (AIC = 56,996 vs. 56,990, respectively) and did not affect the shape of the dose response (data not shown); time-since-exposure models were not further considered.

City Effect

There was no evidence of a difference in effect due to city in the baseline rates ($P > 0.50$). Allowing city to modify the radiation effect resulted in little improvement in fit ($P = 0.28$). The radiation effect for Nagasaki was estimated to be 12% lower than that in Hiroshima (95% CI: –30% to 10%).

Dose-Response Shape

Assuming a linear dose response for both males and females with sex-common age at exposure but sex-dependent attained-age effect modification, and multiplica-

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TABLE 6
Estimated Sex-Specific ERR Linear Dose Coefficients and Confidence Intervals (and for Males, Linear-Quadratic Dose Coefficients) over Selected Dose Ranges

	Linear[a]		Linear-quadratic:[b] males only		
Dose range	Females (95% CI)	Males (95% CI)	Linear (95% CI)	Quadratic (95% CI)	Curvature (σ) (95% CI)
Full range	0.64 (0.52 to 0.77)	0.27 (0.19 to 0.37)	0.09 (–0.03 to 0.23)	0.11 (0.04 to 0.20)	1.3 ($P_{curve} = 0.002$[c])
0–2 Gy	0.65 (0.52 to 0.78)	0.25 (0.17 to 0.36)	0.02 (<–0.05 to 0.18)	0.18 (0.07 to 0.30)	7.2 ($P_{curve} < 0.001$)
0–1 Gy	0.58 (0.44 to 0.74)	0.19 (0.09 to 0.30)	–0.09 (<–0.10 to 0.11)	0.38 (0.12 to >0.41)	–4.4 ($P_{curve} = 0.004$)
0–0.5 Gy	0.53 (0.34 to 0.75)	0.07 (<–0.05 to 0.22)	0.02 (<–0.09 to 0.38)	0.13 (<–0.17 to >0.62)	5.6 ($P_{curve} > 0.5$)
0–0.25 Gy	0.55 (0.24 to 0.92)	0.02 (<–0.18 to 0.25)		$P_{curve} > 0.5$[d]	
0–0.1 Gy	0.39 (–0.27 to 1.1)	0.33 (<–0.10 to 0.89)		$P_{curve} = 0.08$[d]	

[a] Estimated sex-specific excess relative risks (ERR) per Gy using a linear dose-response model over the dose range. All estimates in this table were based on models that included radiation effect modification by attained age (sex-specific), and age at exposure (common to both sexes) and were adjusted for smoking using a multiplicative ERR model for the joint effect of radiation and smoking.

[b] Linear (per Gy) and quadratic (per Gy^2) dose effect estimates in a linear quadratic dose-response model. Only males were allowed to vary using the quadratic model term over the dose range.

[c] P value for a likelihood ratio test of curvature in the male dose response.

[d] Linear-quadratic model parameter estimates unstable due to limited data, results not shown.

tive adjustment for smoking, the estimated linear ERR per Gy was 0.27 (95% CI: 0.19 to 0.37) for males and 0.64 (95% CI: 0.52 to 0.77) for females (Table 6). Of note, these values differ slightly from Table 5 due to the added sex-specific effect modification by attained age. The dose response, however, exhibited statistically significant ($P = 0.03$) upward curvature (i.e., the ratio of quadratic to linear terms) in a linear-quadratic dose-response model that assumed common curvature for males and females. The common curvature (σ) was estimated to be 0.22 per Gy (95% CI: 0.01 to 0.60). The linear dose coefficients for males and females were 0.21 (95% CI: 0.12 to 0.31) and 0.49 (95% CI: 0.33 to 0.67), respectively (data not shown).

Allowing the curvature to differ for males and females led to a further statistically significant improvement in fit ($P = 0.02$ compared to the common curvature model and $P = 0.007$ compared to the linear model). For males, the linear dose coefficient was 0.087 (95% CI: –0.03 to 0.23) with a quadratic estimate of 0.11 (95% CI: 0.04 to 0.20) resulting in a curvature estimate of 1.3 ($P_{curve} = 0.002$). For females, the linear estimate was 0.57 (95% CI: 0.40 to 0.77) with a quadratic estimate of 0.049 (95% CI –0.06 to 0.16) and a curvature estimate of 0.084 ($P_{curve} = 0.39$). Thus, while the dose response for females was consistent with linearity, for males it exhibited significant upward curvature. The plots in Fig. 4 compare the sex-specific fitted linear and linear-quadratic dose-response functions for males and females over the full range of doses. The plots also include nonparametric estimates of the ERR for the 22 dose categories (with the <0.005 category used as the baseline), along with smoothed nonparametric estimates with pointwise confidence bounds (the sex-specific categorical ERR estimates and 95% CIs are shown in Appendix E). Figure 5 shows the same data restricted to doses less than 1 Gy. In males, but not females, the ERR at low doses is markedly less than that predicted by the linear model.

As in earlier LSS reports (*1*, *2*, *4*), a series of analyses were performed to investigate the low-dose linear slope and evidence of curvature in data restricted over various dose ranges. Table 6 summarizes the results of these analyses separately for males and females.

For females, the ERR per Gy estimates were quite similar for all the dose ranges considered. For males, the linear model ERR estimate on the 0 to 0.1 Gy range (0.33), while quite uncertain, was higher than the estimate over the full range (0.27) and had the highest point estimate of any dose range. This suggests that the upward curvature in the dose response for males is largely driven by the rather flat dose response in the range of 0.20–0.75 Gy; the linear ERR per Gy estimates were 0.02 for the 0–0.25 Gy range and 0.07 for the 0–0.5 Gy range. This pattern can be seen in the categorical and smoothed dose-response estimates illustrated in Fig. 5. The linear-quadratic model in men offered no statistical improvement over a purely quadratic model over the full dose range ($P = 0.11$).

Examination of Threshold

The evidence of a threshold dose below which there was no dose response was examined using linear-quadratic threshold models for males and linear threshold models for females. There was no evidence of a threshold for females (estimated threshold dose of 0.08 Gy). This was not significantly different from 0 ($P = 0.18$) and the upper 95% confidence bound was 0.2 Gy. For males, the best estimate for a threshold dose was 0.75 Gy. Similarly, this was not significantly different from 0 ($P = 0.49$). However, the upper 95% confidence bound for the male threshold was considerably larger than that for females (0.8 Gy). The proximity of the best estimate and upper bound among males reflects a bimodal likelihood profile that declines rapidly after the higher dose peak.

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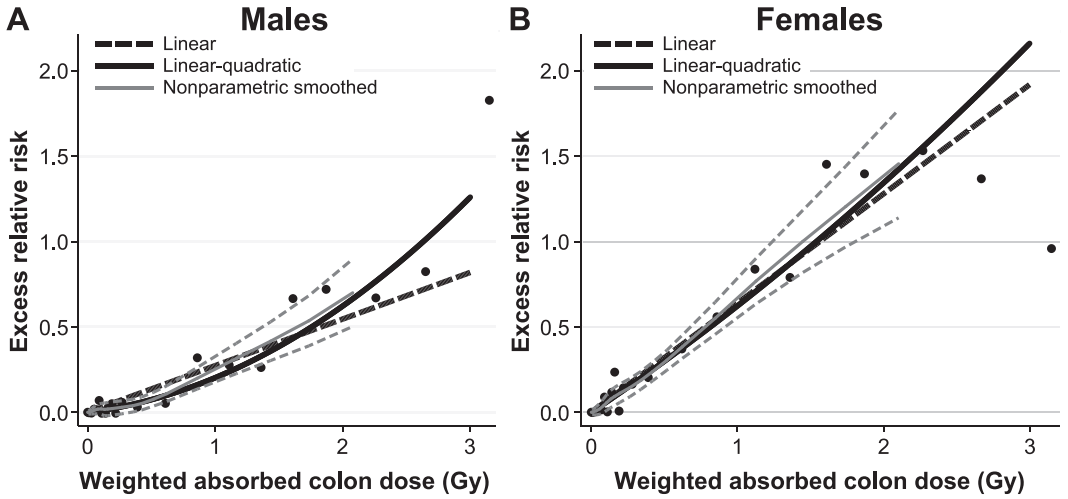


FIG. 4. Panels A and B: Solid cancer dose-response functions for males and females (full dose range). Fitted linear (black dashed line) and linear-quadratic (black solid curve) ERRs for all solid cancers using linear and linear-quadratic dose-response functions for males and females. Also shown are ERR estimates for all 22 dose categories (points) and a nonparametric smoothed estimate (solid gray curve) with point-wise 95% confidence intervals (dashed gray curves). The ERRs are given for subjects at attained age of 70 years after exposure at age 30 years.

EAR Models

Smoking EAR model. Both radiation and smoking effects can also be described using the excess (absolute) risk (rate difference). To adequately model the EAR for smoking, it was necessary to include attained age, sex and birth cohort effects in the smoking term; these effect modifiers were not necessary in the ERR_{smk} model.

Radiation EAR model. Table 7 provides the excess-rate-model parameter estimates and confidence bounds for the EAR model. The radiation EAR for both males and females increased with increasing attained age but the sex difference was only marginally significant ($P = 0.08$). However, to be consistent with the ERR model, we allowed for sex-specific attained-age modifiers. Figure 6A shows the pattern of the excess rates with attained age for males and females exposed at ages 10, 30 and 50, while Fig. 6B displays the age dependence of the female-to-male EAR ratio at 1 Gy. This ratio tended to decrease with increasing attained age. For the same age, the female-to-male EAR ratio also varied with dose due to the nonlinear dose response for males. The latter variability was similar to that seen for the ERR (Fig. 7). The female EAR estimate was 54.7 excess cases per 10,000

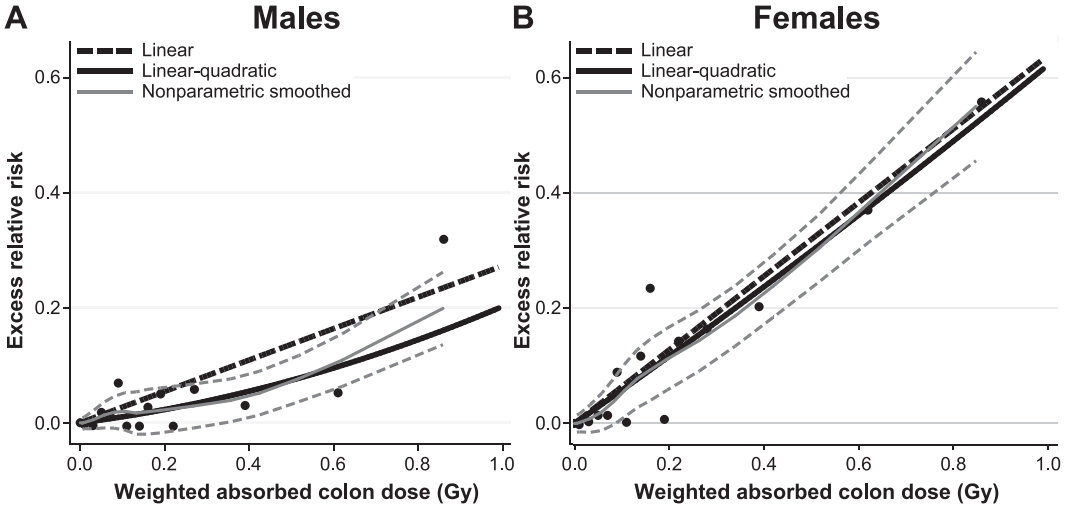


FIG. 5. Panels A and B: Solid cancer dose-response functions for males and females (0–1 Gy). Fitted linear (black dashed line) and linear-quadratic (black solid curve) ERRs for all solid cancers using linear and linear-quadratic dose-response functions for males and females over the range of 0–1 Gy. Also shown are ERR estimates for 15 visible dose categories (points) and a nonparametric smoothed estimate (solid gray curve) with point-wise 95% confidence intervals (dashed gray curves). The ERRs are given for subjects at attained age of 70 years after exposure at age 30 years.

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TABLE 7
Parameter Estimates and Confidence Intervals in Preferred Excess Relative and Excess Absolute Risk Models: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

	Males				Females		Both sexes
	Dose effect[a]			Attained age (power)	Dose effect[a]	Attained age (power)	
	Linear[c]	Quadratic	Curvature[d]		Linear[c]		Age at exposure[b]
				All solid cancers			
ERR model							
Estimate	0.094	0.11	1.16	–2.70	0.64	–1.36	–22%
(95% CI)	(<0.02 to 0.23)	(0.04 to 0.19)	$P = 0.002$	(–3.58 to –1.81)	(0.52 to 0.77)	(–1.86 to –0.84)	(–30% to –13%)
EAR model							
Estimate	21.7	21.2	0.98	2.89	54.7	2.07	–30%
(95% CI)	(<–1.7 to 47.7)	(6.8 to 37.6)	$P = 0.003$	(2.14 to 3.68)	(44.7 to 65.3)	(1.64 to 2.53)	(–37% to –22%)
				Non-sex-specific cancers			
ERR model							
Estimate	0.036	0.12	3.42	–3.21	0.64	–1.79	–19%
(95% CI)	(<0 to 0.16)	(0.06 to 0.21)	$P < 0.001$	(–4.18 to –2.26)	(0.51 to 0.79)	(–2.39 to –1.18)	(–29% to –8%)
EAR model							
Estimate	7.86	24.3	3.09	2.40	40.6	2.30	–26%
(95% CI)	(<–12 to 30.9)	(10.9 to 40)	$P < 0.001$	(1.62 to 3.19)	(31.7 to 50.0)	(1.74 to 2.88)	(–35% to –17%)

[a] The linear parameter in the multiplicative ERR model is the ERR per Gy at age 70 after exposure at age 30 years. For the EAR model this parameter is the excess cases for 10,000 person-years per Gy at age 70 after exposure at age 30 years. The curvature is the ratio of the quadratic term to the linear term and has units of 1/Gy. The quadratic parameter is equal to the product of the linear term and curvature.
[b] Percentage change per decade increase in age at exposure (common to males and females).
[c] Radiation associated excess per one Gy for ERR and per 10,000 person-years per Gy for EAR.
[d] Ratio of quadratic to linear coefficient (per Gy).

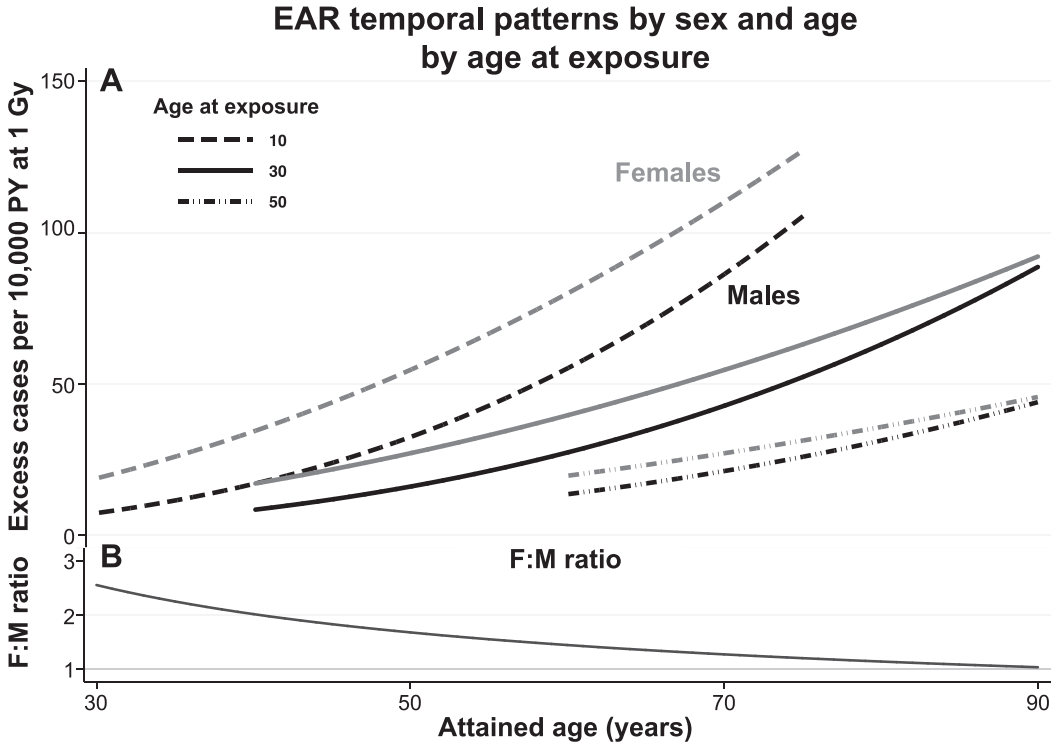


FIG. 6. Solid cancer excess rates (EARs) at 1 Gy by attained age, sex and age at exposure. Panel A: Excess absolute rates at 1 Gy as a function of attained age for males (black curves) and females (gray curves) exposed at ages 10 years (dashed), 30 years (solid) and 50 years (dash-dot). Panel B plots the female-to-male (F:M) EAR ratio at 1 Gy as a function of attained age.

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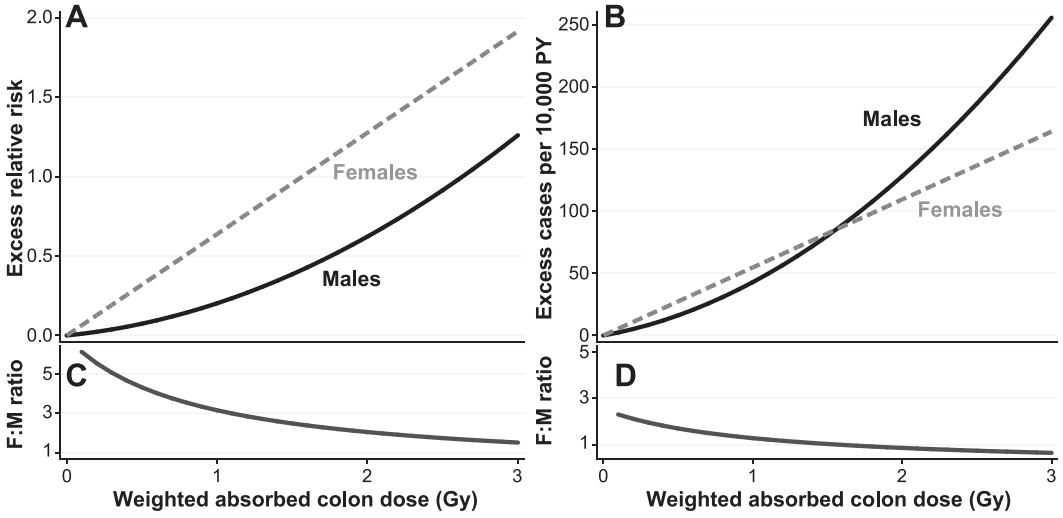


FIG. 7. Preferred ERR and EAR models by sex. The dose-response functions in the preferred ERR (panel A) and EAR (panel B) models are shown. Panels C and D show the female-to-male (F:M) risk ratio versus dose. The dose-response curves are shown for subjects at attained age of 70 years after exposure at age 30 years.

person-year-Gy (95% CI: 44.7 to 65.3), while for males the total of the linear and quadratic excess cases at 1 Gy was 42.9 (21.7×1 Gy $+ 21.2 \times 1$ Gy^2) per 10,000 person-year-Gy. These values were very similar to the 2007 analysis, which reported 60 and 43 excess cases per 10,000 person-year-Gy for females and males, respectively. The previously reported age-at-exposure modifier was –24% per decade increase while attained age was modified to the power of 2.38 (*4*) and were similar to the current estimates.

As with the ERR model, there was evidence of statistically significant upward curvature in the EAR dose-response model for males ($P = 0.003$), but no indication of such curvature for females ($P = 0.38$). The magnitude of the curvature parameter in the male dose response was 0.98, which was similar to that seen in the ERR model (1.16). The curvature in the EAR dose response for males differed significantly from that for females ($P = 0.04$).

Summary of Preferred Models

Based on the analyses described above, we developed ERR and EAR models that provided summaries of the nature of the radiation-associated solid cancer risks seen over the entire follow-up period. These models are more complex than those reported in earlier analyses of the LSS incidence or mortality data. There is now evidence that sex differences in the excess radiation risks for males and females can no longer be captured by using a simple dose-independent sex ratio due to the significant upward curvature exhibited in males but not in females and a more rapid decrease of ERR with attained age in males compared to females.

The upper half of Table 7 presents the parameter estimates for the radiation effects in our preferred smoking-adjusted ERR and EAR models for all solid cancers in aggregate. All estimates are for a person exposed at age 30 with an attained age of 70. Combining linear and quadratic risk estimates for males results in an ERR of 0.20 (Wald 95% CI: 0.12 to 0.28) at 1 Gy and an ERR of 0.010 (Wald 95% CI: –0.0003 to 0.02) at 0.1 Gy. The respective ERR estimates for women were 0.64 and 0.064, resulting in female-to-male ERR ratios of 3.2 at 1 Gy and 6.1 at 0.1 Gy. The EAR estimate at 1 Gy among males was 42.9 (Wald 95% CI 27 to 58) excess cases per 10,000 person-years at 1 Gy and 2.4 (Wald 95% CI: 0.21 to 4.6) excess cases per 10,000 person-years at 0.1 Gy. On the EAR scale, the F:M ratios were 1.3 at 1 Gy and 2.3 at 0.1 Gy. The sex-specific risk estimates and F:M ratios for the ERR and EAR models are shown in Fig. 7.

Preferred Models: Risk Estimates of Non-Sex-Specific Cancers

Cancers unique to the sexes may affect the F:M ratios on both the relative and additive scales due to varying background rates and possible differences in radiation sensitivity. We therefore performed an analysis using the preferred models while restricting it to non-sex-specific cancers. Cancers excluded from the analysis included: breast, ovary, uterus and other female-specific cancers among women, and prostate, testicular, male breast and other male-specific cancers among men. A total of 18,555 non-sex-specific solid cancers were observed and modeled in aggregate.

The lower half of Table 7 shows that the ERR for females was unchanged after restricting cases to non-sex-specific cancers. The P value for curvature among females decreased to 0.11 (not shown). For men, the estimated curvature increased as the linear parameter decreased. The F:M ratio was 4.0 at 1 Gy and greater than 10 at 0.1 Gy. On the EAR scale, the F:M ratio was 1.3 at 1 Gy and 3.9 at 0.1 Gy with strong evidence of curvature among males. Although there was some evidence of curvature among females, it was significantly less than that observed in males ($P = 0.02$). A more detailed discussion of sex-specific versus non-sex-specific responses is given in Appendix G.

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TABLE 8
Observed and Fitted Cases by Dose Category and Sex for an Excess Relative Risk Model with a Linear-Quadratic Radiation Dose Response for Males and Linear for Females: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

Dose category (Gy)	Subjects	Person-years	Cases	Background	Radiation only	AF[a] radiation	Radiation-smoking interaction[b]	AF[a] radiation-smoking[b]	Smoking only	AF[a] smoking
Both males and females										
<0.005	61,217	1,794,130	12,592	10,646.4	3.3	0%	0.2	0%	1,857.2	15%
–0.1	27,511	807,885	5,674	4,785.3	81.8	1%	6.1	0%	867.3	15%
–0.2	5,594	164,111	1,217	996.4	79.7	7%	6.1	1%	179.2	15%
–0.5	5,926	169,177	1,414	1,023.3	187.7	13%	15.9	1%	190.5	13%
–1	3,136	88,992	889	526.0	228.0	26%	22.0	2%	98.8	11%
–2	1,565	42,236	560	239.1	211.0	38%	29.4	5%	54.0	10%
2+	495	12,953	192	67.0	103.6	54%	17.2	9%	15.6	8%
Total	105,444	3,079,484	22,538	18,283.5	895.0	10%[c]	96.9	1%[c]	3,262.6	15%[c]
Males										
<0.005	25,062	666,525	6,012	4,251.0	0.3	0%	0.1	0%	1,710.2	28%
– 0.1	11,175	302,141	2,635	1,884.3	10.3	0%	3.9	0%	778.4	30%
– 0.2	2,132	57,898	497	370.5	9.6	2%	3.7	1%	154.2	31%
– 0.5	2,301	59,840	599	390.6	26.3	4%	10.0	2%	163.7	27%
– 1	1,282	32,202	382	211.2	42.5	11%	15.9	4%	86.1	23%
– 2	716	17,815	254	111.6	62.3	25%	23.8	9%	47.9	19%
2+	242	5,778	94	32.5	42.1	45%	15.5	16%	14.4	15%
Total	42,910	1,142,200	10,473	7,251.7	193.5	6%[c]	72.9	2%[c]	2,954.9	30%[c]
Females										
<0.005	36,155	1,127,605	6,580	6,395.4	2.9	0%	0.1	0%	147.0	2%
– 0.1	16,336	505,744	3,039	2,901.0	71.5	2%	2.2	0%	88.9	3%
– 0.2	3,462	106,213	720	626.0	70.1	10%	2.5	0%	25.0	3%
– 0.5	3,625	109,337	815	632.6	161.4	20%	5.9	1%	26.7	3%
– 1	1,854	56,790	507	314.8	185.5	37%	6.1	1%	12.7	3%
– 2	849	24,420	306	127.5	148.7	49%	5.6	2%	6.1	2%
2+	253	7,175	98	34.5	61.6	63%	1.7	2%	1.3	1%
Total	62,534	1,937,284	12,065	11,031.8	701.5	13%[c]	24.0	0[c]	307.7	3%[c]

[a] AF = attributable fraction (cases estimated to be attributable to that exposure over the total number of cases in that category).
[b] Since the effects of radiation and smoking were modeled as multiplicative, some cases are associated with the radiation-smoking interaction.
[c] Among those exposed to ≥0.005 Gy

Preferred ERR Model: Observed and Fitted Cases

Table 8 provides information on the observed and fitted number of cases by dose category and sex for the preferred ERR model (linear-quadratic for males and linear for females) and a multiplicative joint effect of radiation and smoking. The total estimated number of radiation-associated cancers was 992 (266 for males and 726 for females), calculated by adding the ''radiation only'' and ''radiation-smoking'' interaction columns in Table 8. The corresponding attributable fractions for people exposed to at least 5 mGy were 6% for males, 13% for females and 10% for both sexes combined. Smoking was associated with 15% (3,360 cases) of the solid cancer cases in the cohort, with attributable fractions of 30% for males and 3% for females. Estimates of fitted cases from alternative models are shown in Appendix D.

SUMMARY AND DISCUSSION

This analysis of the LSS solid cancer incidence data includes more than 50 years of follow-up through 2009, 64 years after the atomic bombings in Hiroshima and Nagasaki. Several significant changes have occurred since the previously reported study (*3*). During the 11 additional years of follow-up, the surviving proportion of the cohort dropped from 52% to 36% while 5,090 new incident cancer cases were observed. Dose estimates were improved using more accurate information on the survivors' locations and shielding characteristics at the time of the bombings. In assessing the radiation dose response, we considered effects of smoking, a major non-radiation cancer risk factor, as well as established risk modifiers, such as attained age, age at exposure and sex. We updated and extended the migration coefficients used for adjusting strata-specific person-years. Also, as explained in greater detail in Appendix A, we removed a surveillance bias on the age-at-exposure effect induced from cases diagnosed solely by autopsy.

While these analyses revealed provocative results regarding the shape of the dose response, the most fundamental finding was that a single, acute whole-body exposure to ionizing radiation continued to increase solid cancer risks even after 50 years. Although on a relative scale, radiation-related risks tended to decrease with increasing attained age, the decrease was not due to any lessening of the effect of exposure but rather due to increasing background cancer rates. On an absolute (EAR) scale, the excess rates increased with

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increasing attained age in both males and female (Fig. 7). The overall attributable fraction of cases due to radiation exposure was 10%, which is very similar to the value (11%) reported by both Preston *et al*. in 2007 (*4*) and Thompson *et al*. in 1994 (*2*). These values are a few percentage points higher than for the attributable fraction observed in the previous mortality studies, which have also been quite consistent at approximately 8% among those with non-zero doses (*1*, *19–21*).

While previous LSS solid cancer incidence data demonstrated linear dose responses for both males and females, the current analyses demonstrated significant upward curvature for males with little indication of nonlinearity for females. It should be noted that the latest published LSS mortality report, by Ozasa *et al*. (*1*), presented evidence of curvature in the ERR dose response over the dose range 0–2 Gy for all solid cancer, which was not evident over the full dose range. Ozasa *et al*. further reported that the evidence of curvature under 2 Gy had increased with the longer follow-up periods, with the most recent eight years of follow-up between 1995 and 2003 changing the *P* value for curvature from 0.16 to the statistically significant value of 0.02. Preliminary analyses of more recent solid cancer mortality data continue to suggest curvature, perhaps in both sexes. Due to the differences in fatality for some cancers, there are inherent differences in the mix of cancer types between incidence and mortality data, but results from dose-response analyses that have aggregated all solid cancers have been broadly comparable (*22*).

We investigated several factors that may explain the current curvature findings in the dose response for solid cancer incidence, particularly among males. First, since the current cancer incidence data differed from the previous data (*4*) in several ways, we compared results of the current analysis with those from analyses with no smoking adjustment, with follow-up restricted through 1998 and with autopsy-only cases included as in the previously reported study (*4*). We further tested the impact of removing the NIC group from the analysis. These comparisons were done using both the DS02R1 and DS02 doses, and for the full dose range and the 0–2 Gy dose range. The detailed results of these comparisons are given in Appendix F. The revised dose estimates consistently strengthened the evidence of curvature in all the analyses and generally had more impact on curvature than other changes to the data. We note that all changes made to update the doses were done without regard to the sex of the survivor. Among males, regardless of the dosimetry version used, the extended follow-up also strengthened the evidence of curvature over both the full and restricted-dose ranges. However, evidence of curvature was already present in analysis restricted to 1998 when the new doses were used. Censoring the autopsy-only cases slightly strengthened the evidence of curvature. Excluding the NIC cohort members had little effect on either the risk estimates or curvature inferences. Regardless of the dosimetry version used, adjustment for smoking had virtually no effect on curvature over the full or restricted dose ranges. Among females, there was no statistical evidence of curvature in any of these analyses, however, the updated DS02R1 dosimetry as well as analyses restricted to the 0–2 Gy range generally tended to decrease *P* values when testing curvature.

We also investigated the extent to which different cancer types may influence the overall and sex-specific shape of ERR dose responses for solid cancer incidence. Appendix G details the shape of ERR dose responses in several subsets, including: sex-specific/non-sex-specific cancers; smoking-related/nonsmoking-related cancers; and gastrointestinal (GI) tract cancers/non-GI cancers. Removal of sex-specific cancers tended to strengthen the evidence of curvature among females, especially in the 0–2 Gy range where we observed statistically significant upward curvature ($P_{\text{curve}} = 0.01$). The dose response for sex-specific cancers showed no evidence of curvature in either sex over the full or restricted dose ranges. The proportion of sex-specific cancers differed in males and females (9 vs. 26%, respectively). For smoking-related cancers there was no evidence of curvature in either sex over the full range but evidence of curvature in both sexes over the restricted range. For nonsmoking-related cancers, only males showed evidence of curvature while there was none among women. Over the full dose range, there was evidence of curvature in males for both GI and non-GI cancers but not among females. Over the 0–2 Gy dose range the evidence of curvature in males was not significant for GI cancers ($P = 0.27$). Male non-GI cancers included a smaller proportion of sex-specific cancers (21%) than female non-GI cancers (47%). These findings suggest that the sex difference in the dose-response shape for all solid cancer as a group may more likely be a consequence of heterogeneity in the shape of the dose response for different cancer sites coupled with a differential distribution of the sites by sex, than to reflect some more general sex-related mechanism. Site-specific radiation dose-response shapes may vary by cancer site because of the involvement of risk modifiers, known or unknown, or possibly reflect different biological responses of organs/tissue involved.

Pooling all solid cancers offers the advantage of large numbers to enhance statistical precision when assessing the dose response, especially at low doses, and investigating effect modification of the radiation risk by age, time, sex and other factors. Pooling of all solid cancers is particularly relevant for the atomic bomb survivors, who received whole-body exposure and among whom radiation effects are indicated for virtually all organ sites. Aggregate solid cancer risks have been traditionally reported in both cancer incidence and cancer mortality risks from the LSS and other cohorts. However, there are also limitations to such an approach because there may be real differences in the magnitude of radiation risk and nature of effect modification across different cancer sites. Subsequent LSS solid cancer reports in this series will provide detailed analyses of radiation dose responses for site-specific cancers and related cancer types, focusing on how the dose response and modifying effects are affected by smoking and other relevant lifestyle factors. Additional reports will include

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respiratory cancers, upper and lower digestive cancers, male and female sex-specific cancers, among others. Lifestyle factors for these analyses include self-reported alcohol consumption, educational background, reproductive history, medical history and dietary intake.

The current data also provide new insights into the temporal pattern of the all-solid cancer risk. That is, the ERR per Gy decreased with attained age more rapidly for males than females. Also, the EAR per 10,000 person-year-Gy increased slightly more rapidly for males than females. Consequently, sex ratios for the ERR and EAR were attained-age dependent as well as dose dependent because of the curvature in dose response for males. Both ERR and EAR decreased with increasing age at exposure. The ERR for males was considerably lower than that for females at any dose, which may be due primarily to lower background rates of cancer incidence among females. On the other hand, while excess rates for males were lower than those for females for doses less than approximately 1.5 Gy, males had higher excess rates than females at higher doses. This comparison of alternative measures of the radiation excess highlights the importance of considering the effects of radiation on both relative and absolute scales. The analyses of non-sex-specific cancers as a subgroup showed that the EARs were consistently lower for males compared to females, particularly at lower doses. The latter finding is a slight departure from the previously reported study, which showed similar EARs across the sexes.

In analyzing the modifying effect of age at exposure on the radiation risk, special attention was given to the potential effect of cancers diagnosed only through autopsy examinations (''autopsy-only cases''). The investigation was prompted by the U-shaped pattern of the ERR per 1 Gy for solid cancer by age at exposure, as reported in our previous published study (*4*) and recognized by the BEIR VII (*23*). As explained in Appendix A, ''occult'' cases had been censored in the report by Thompson *et al*. (*2*), while no such censoring was performed by Preston *et al*. (*4*). The occult cases were most often detected at autopsy. We made a more general decision to censor all cases that had been determined only due to postmortem exam. After censoring these autopsy-only cases, the U-shaped response no longer appeared and could be rejected statistically. Instead, a simple log-linear model was used.

Although we decided to use a simple multiplicative model for the radiation-smoking joint effects on the ERR, the choice of smoking adjustment model (multiplicative or additive) had little impact on the shape of radiation dose response or modifying effect of age at exposure or attained age, which indicates that the radiation risk estimates are not strongly confounded or otherwise modified by smoking. The use of the multiplicative model for smoking adjustment allows for comparison with the previous LSS data unadjusted for smoking. The current estimate of 992 radiation-associated solid cancer cases among the 22,538 eligible first primary solid cancers is 139 more than in the previously reported analysis. Approximately 3,360 of the solid cancers were estimated to be associated with smoking.

The current LSS solid cancer incidence risk estimates can be compared to those from other populations with whole-body exposure. The latest analysis of mostly male nuclear workers (mean dose, 0.021 Gy) in France, the United Kingdom and the United States (INWORKS) reported a linear estimate of ERR per Gy of 0.47 (90% CI: 0.18 to 0.79) for solid cancer mortality, unadjusted for smoking (*24*). This is comparable to our linear ERR estimate of 0.36 per Gy (95% CI: 0.28 to 0.45) for males at age 70 after exposure at age 30 (Table 5, first line). However, the male risk in the LSS at 100 mGy using our preferred linear-quadratic ERR model (Table 7) was estimated to be 0.01, which was lower than that of 0.047 linearly scaled to 100 mGy from the INWORKS data. In the Techa River cohort of residents with low-dose exposure to radioactive materials from contaminated river and soil, the sex-averaged ERR for solid cancer incidence was estimated to be 0.077 per 100 mGy (95% CI: 0.013 to 0.150) after adjustment for smoking (*25*). Again, this was comparable to our linear, smoking adjusted, sex-averaged ERR estimate of 0.047 per 100 mGy (95% CI: 0.039 to 0.055) (Table 5, last line; scaled to 100 mGy). The Mayak Production Association workers (75% male) had mixed exposure to gamma rays and plutonium (Pu) but had fractionated gamma exposures in the dose range similar to the LSS; the linearly estimated ERR for external gamma-ray exposure adjusted for Pu dose was 0.12 per Gy (95% CI: 0.03 to 0.21) for solid cancer mortality (*26*) or an ERR of 0.07 (95% CI: 0.01 to 0.19) per Gy for solid cancer unadjusted for Pu exposure (*27*). Both studies excluded cancer sites primarily related to Pu exposure (i.e., lung, liver and bone). These estimates are lower than our linear estimates. We note the LSS male dose response over the lowest dose range considered (0–100 mGy) tended to be considerably greater than the estimates that consider broader dose ranges (Table 6). This highlights the uncertainties in the shape of the dose response in the current analyses. These uncertainties taken together with inconsistencies with prior LSS analyses and the findings from other studies precludes definitive conclusions that might confidently guide the development of modified radiation protection policies at this time.

More than six decades after the atomic bombs, solid cancer continues to be the major documented health detriment attributed to radiation exposure in the atomic bomb survivors. The excess risk of solid cancer persists and will likely persist throughout the atomic bomb survivors' lifetimes. As of 2009, the average age of the LSS cohort was 78 years, with those still alive exposed at the youngest ages. Many incident cancers are predicted in the next 10–15 years. Critical questions regarding the long-term risk among the youngest survivors are yet to be answered, and may have significant bearing on the dose response and temporal patterns of radiation risk. New trends may have begun to emerge. Upward curvature in the dose response, previously observed in the mortality data, are now evident in the incidence data, especially in males. Females also show some evidence of curvature in the dose response of non-sex-specific cancers, particularly over the 0–2 Gy range. There

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is also evidence of sex-dependent modifying effects of attained age on ERR and EAR.

Despite the long follow-up of this cohort, our understanding of radiation-related cancer risk is still evolving, leading to new unresolved questions. For example, will curvature emerge in the dose response of females in the future? Does the sex difference in the shape of dose response for solid cancer incidence reflect the heterogeneity of dose responses among different organs and distribution of the cancers in males and females, or is it dependent on other factors? A number of organ-specific investigations are underway that may help to provide answers to these questions. We also plan to investigate the impact of the zero-dose comparison group along with a deeper exploration of the effect of the updated dosimetry. As these issues evolve and undergo further investigation, we urge caution with the interpretation of the curvature findings and the conclusions that may be drawn from the current data.

APPENDICES

Appendix A: Exclusion of Autopsy-Only Cases and Impact on Age-at-Exposure Effect Modification

As Ron *et al*. reported in 1994 (*28*), autopsy rates varied markedly with both radiation dose and calendar year. Appendix fig. A1 shows the proportion of autopsied deaths by calendar year and radiation dose among the LSS cohort members analyzed in this study (n = 105,444). Autopsy-only (AO) cases inflate cancer rates since they include asymptomatic cancers that were not otherwise documented. Since AO cases occurred more often among those with higher radiation doses and exposed at older ages (i.e., those persons dying in the 1960s), their inclusion appears to have artificially increased radiation risks among those exposed at older ages.

Cancer cases were defined as AO cases when the diagnosis was based solely on the results of an autopsy that included microscopic tissue examinations and when there were no clinical diagnoses of cancer before or at death. No DCO cases appeared among the AO cases because postmortem examinations occur after the reporting of the death by a certifying physician. Thompson *et al*. excluded ''occult'' cancers (''...small tumors that were usually diagnosed incidentally at autopsy.''; n = ''not reported'') (*2*). Preston *et al*. included both AO cases as well as occult cancers while noting that AO cases accounted for less than 4% of cases (*4*). Many of the AO cases in the current data overlap with early occult cancers. Of the 206 occult cancers that occurred among the 23,158 otherwise eligible cases, 179 (87%) were considered AO cases and excluded. In total, we censored 620 AO cases (2.7%), leaving us a total of 22,538 cases to analyze. Of the 620 AO cases, 111 (17.9%) were thyroid, 110 (17.7%) were stomach, 79 (12.7%) were lung and 64 (10.3%) were prostate cancers. Each other individual site accounted for less than 10% of the total AO cases. We believe that the AO designation, rather than the ''occult'' definition used by Thompson *et al*., is more specific to the ascertainment bias and we therefore decided to censor AO cases. All cases identified via autopsy were excluded from a recent analysis of thyroid cancer by Furukawa *et al*. (*29*).

A notable finding, reported in the previous LSS incidence study (*4*), was a U-shaped curve for radiation risk based on age at exposure. Censoring the AO cases has a marked effect on inference about the effect of age at exposure on radiation risks. Appendix fig. A2 compares the age-at-exposure effect modification using the current dataset using a linear ERR model (same model as shown in the bottom line of Table 5) with and without censoring of the AO cases. When the AO cases were included, a

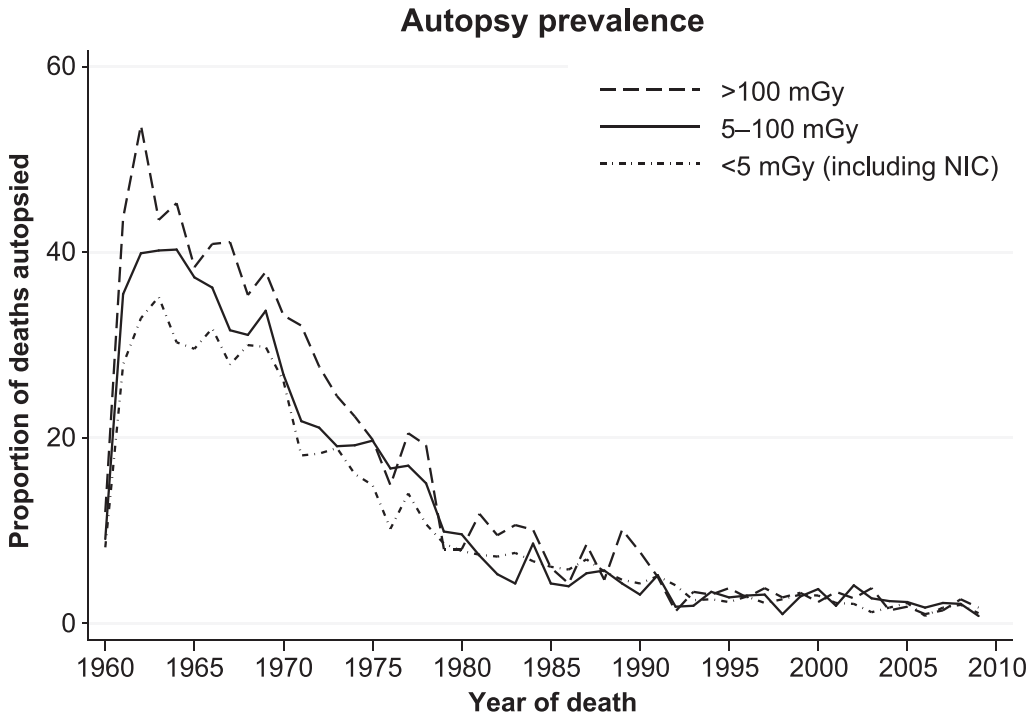


FIG. A1. Proportion of deaths autopsied by year of death and colon dose categories. The autopsy program was very active primarily in the 1960s. Those dying in that decade tended to be older at the time of the bombing. More autopsies were performed on those populations exposed to higher doses, particularly in the 1960s and 1970s.

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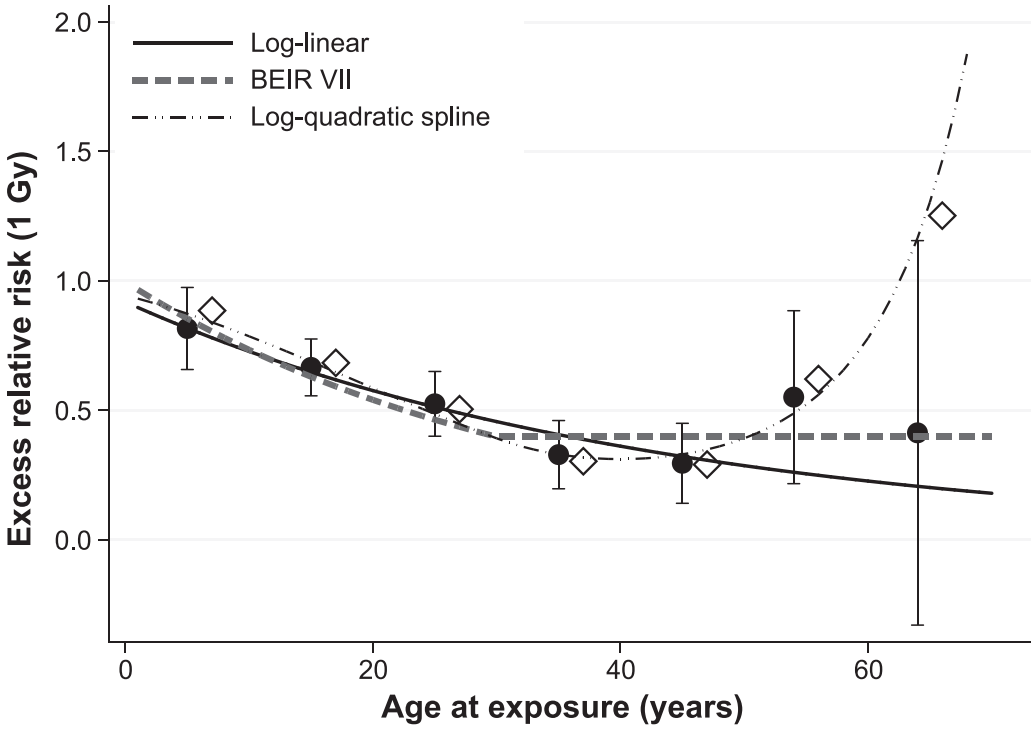


FIG. A2. Age-at-exposure effects on radiation risk and the impact of autopsy-only cases. Sex-averaged ERR estimates at 1 Gy in linear ERR models as a function of age at exposure at attained age of 70 years. Black solid dots are nonparametric estimates when excluding autopsy-only cases (with Wald 95% confidence intervals). Open gray diamonds (offset two years to the right to avoid overlap) show nonparametric estimates when including autopsy-only cases. The dot-dash line shows a quadratic spline model fit while including autopsy-only cases. The solid black line shows a standard log-linear fit to the data when excluding autopsy-only cases. The gray dashed line represents a model where the ERR can decrease in a log-linear fashion to age at exposure = 30 years with no further changes for those exposed later in life (adopted by the BEIR VII report). After censoring the autopsy-only cases, the quadratic spline (dot-dash line) could be statistically rejected compared to the log-linear model. The BEIR VII model did not fit the data statistically better than the log-linear model. The log-linear model was used throughout this article.

U-shape curve was observed. However, after censoring the AO cases, there was no evidence of curvature ($P > 0.50$). Note also that while censoring the AO cases changed the age-at-exposure effect modification for those exposed at older ages, there was little difference for those exposed at younger ages. Furthermore, overall radiation risk estimates were only minimally affected by the inclusion status of AO cases, as shown in appendix table F1. Given these findings, we believe that the U-shaped curve was an artifact of the inclusion criteria of the previously reported analysis, and we have therefore censored the AO cases and used a standard log-linear model for the age-at-exposure effect throughout this article. We also note that the BEIR VII (*23*) model had approximately the same fit as did the log-linear model (change in deviation = 1.8). No interactions of the age-at-exposure effect modification were evident with sex ($P > 0.5$) or city ($P > 0.5$).

Appendix B: Migration Adjustments

Because Japan does not have a national cancer registry system, incident cancers that occurred outside of the catchment areas of the Hiroshima and Nagasaki cancer registries were not systematically ascertained. To avoid bias (particularly in EAR models) resulting from underrepresentation of cases, person-years were adjusted to account for migration. The estimates of in- and out-migration were derived from our clinical contacting program. The ABCC/RERF Adult Health Study consists of a cross section of the LSS (but generally excludes the NIC group) and is run in parallel in Hiroshima and Nagasaki. The AHS includes biennial visits to RERF's clinic at which time the subjects' addresses are routinely confirmed. Participating subjects are contacted by telephone and postcard. Address information for LSS subjects, other than those who are AHS participants, may have been available from other sources, including mail surveys, reports of cancer diagnoses to the tumor registries and death certificates. We used all such sources to organize individual histories of addresses through the follow-up period to predict stratum-specific probabilities of residing in the AHS visitor areas using logistic regression based on city, sex, five-year categories of birth year and calendar year period in a manner similar to that described by Sposto, *et al*. (*30*). These probabilities were then used as a surrogate for the residence probabilities of the full LSS cohort and applied to the tabulated person-year data used for the full analysis to reduce stratum-specific person-years.

Probabilities of out-migration tended to be higher for males compared to females, higher for younger birth cohorts during middle age and higher for persons from Nagasaki than those from Hiroshima. The two previous major incidence reports used the values as calculated by Sposto *et al*., which were through 1987. In the 2007 study reported by Preston *et al*. (data through 1998), the estimates derived from the period through 1987 were carried forward without adjustment. The current analysis updated the underlying data through 2005 and migration estimates were carried forward for the last four years of the analysis without adjustment.

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Appendix C: Cancer Diagnoses

Appendix Table C1
Number of Solid Cancer Cases by Cancer Site and Sex among the LSS Subjects, 1958–2009

	Sex					
	Male		Female		Total	
Cancer site	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
All solid cancers	10,473	100%	12,065	100%	22,538	100
Oral cavity and pharynx						
Lip	2	0.02%	3	0.02%	5	0.02%
Tongue	63	0.6%	56	0.5%	119	0.53%
Salivary gland	31	0.3%	19	0.2%	50	0.22%
Floor of mouth	10	0.1%	7	0.1%	17	0.08%
Gum and other mouth	38	0.4%	53	0.4%	91	0.40%
Nasopharynx	11	0.1%	9	0.1%	20	0.09%
Tonsil	9	0.1%	3	0.02%	12	0.05%
Oropharynx	14	0.1%	5	0.04%	19	0.08%
Hypopharynx	53	0.5%	3	0.02%	56	0.25%
Other oral cavity and pharynx	5	0.05%	0	0%	5	0.02%
Digestive system						
Esophagus	394	3.8%	92	0.8%	486	2.2%
Stomach	3,090	29.5%	2,571	21.3%	5,661	25.1%
Small intestine	15	0.1%	24	0.2%	39	0.2%
Colon	782	7.5%	1132	9.4%	1,914	8.5%
Rectum	512	4.9%	510	4.2%	1,022	4.5%
Anus, anal canal and anorectum	6	0.1%	18	0.1%	24	0.1%
Liver	1,122	10.7%	763	6.3%	1,885	8.4%
Intrahepatic bile duct	44	0.4%	87	0.7%	131	0.6%
Gallbladder	84	0.8%	270	2.2%	354	1.6%
Other biliary	136	1.3%	204	1.7%	340	1.5%
Pancreas	306	2.9%	417	3.5%	723	3.2%
Retroperitoneum	3	0.03%	8	0.1%	11	0.0%
Peritoneum, omentum and mesentery	0	0%	3	0.02%	3	0.01%
Other digestive organs	8	0.1%	18	0.2%	26	0.1%
Respiratory system						
Nose, nasal cavity and middle ear	48	0.5%	50	0.4%	98	0.4%
Larynx	154	1.5%	26	0.2%	180	0.8%
Lung and bronchus	1,445	13.8%	1,001	8.3%	2,446	10.9%
Pleura	1	0.01%	0	0%	1	0.00%
Trachea, mediastinum and other respiratory	3	0.03%	13	0.1%	16	0.1%
Bones and joints						
Bones and joints	13	0.1%	12	0.10%	25	0.11%
Mesothelioma and soft tissue						
Mesothelioma	17	0.2%	10	0.1%	27	0.1%
Soft tissue including heart	21	0.2%	26	0.2%	47	0.2%
Skin						
Melanoma of the skin	10	0.1%	12	0.1%	22	0.1%
Other non-melanoma skin	195	1.9%	321	2.7%	516	2.3%
Breast						
Breast	10	0.1%	1,470	12.2%	1,480	6.6%
Female genital system						
Cervix uteri	–	–	886	7.3%	886	3.9%
Corpus uteri	–	–	244	2.0%	244	1.1%
Uterus, NOS	–	–	121	1.0%	121	0.5%
Ovary	–	–	288	2.4%	288	1.3%
Vagina	–	–	22	0.2%	22	0.1%
Vulva	–	–	37	0.3%	37	0.2%
Other female genital	–	–	11	0.1%	11	0.05%
Male genital system						
Prostate	851	8.1%	–	–	851	3.8%
Testis	18	0.2%	–	–	18	0.1%
Penis	12	0.1%	–	–	12	0.1%
Other male genital	13	0.1%	–	–	13	0.1%

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Appendix Table C1
Continued.

	Sex					
	Male		Female		Total	
Cancer site	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
Urinary system						
Urinary bladder	411	3.9%	215	1.8%	626	2.8%
Kidney and renal pelvis	158	1.5%	134	1.1%	292	1.3%
Ureter	31	0.3%	31	0.3%	62	0.3%
Other Urinary Organs	11	0.1%	17	0.1%	28	0.1%
Eye, brain and central nervous system						
Eye and orbit	2	0.02%	2	0.02%	4	0.00%
Brain	51	0.5%	60	0.5%	111	0.5%
Cranial nerves, other nervous system	48	0.5%	126	1.0%	174	0.8%
Thyroid	72	0.7%	430	3.6%	502	2.2%
Other endocrine including thymus	37	0.4%	34	0.3%	71	0.3%
Other						
Other solid cancers	103	1.0%	191	1.6%	294	1.3%

Appendix D: Smoking Effect Models

Smoking intensity, start and stop dates and cumulative pack-years were calculated based on survey data collected periodically through the follow-up period. Smoking was modeled as a function of cumulative pack-years, intensity, duration and time since quitting. As described in the main text, a linear ERR_{smk} (pack-years) model with modification by duration and intensity was used for smoking and a multiplicative joint effect with radiation was assumed. However, there were other possibilities. In appendix table D1, fitted numbers of cases are shown for alternative models attributed to radiation, smoking and their joint effects.

There was considerable variability in the number of radiation-associated cases for the different models, with the smallest one estimated in our preferred model. The estimated numbers of radiation- and smoking-related cases exhibit less model dependence for females than for males. For males, the number of cases attributed to smoking outnumbers those attributed to radiation. For females, the number of cases attributed to radiation was roughly double the number attributed to smoking, due to the low prevalence of smoking among females in the LSS. This estimate was quite stable regardless of the chosen model. We chose to present estimates using multiplicative smoking-radiation ERR models, since previously reported analyses (that ignored smoking) were implicitly multiplicative (i.e., smoking was subsumed in the background term and multiplied with the radiation ERR).

Appendix Table C2
Mean Age at Diagnosis, Proportions of Histological Confirmation, Death Certificate Only Cases by Major Cancer Site: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

Cancer diagnosis	ICD-10	No. of cases	Mean age at diagnosis	Histological confirmation (%)	DCO[a] (%)
Oral cavity and pharynx	C00–C14	394	65.9	93.9	2.8
Esophagus	C15	486	69.2	81.9	6.6
Stomach	C16	5,661	68.3	81.5	9.0
Colon	C18	1,914	71.3	88.1	6.3
Rectum	C19–C20	1,022	68.6	91.1	4.8
Liver	C22	2,016	68.2	38.6	19.2
Gallbladder	C23–C24	694	73.1	58.5	12.8
Pancreas	C25	723	72.2	42.5	20.8
Lung	C34	2,446	71.6	61.2	14.6
Non-melanoma skin	C44	516	74.5	97.3	1.7
Breast	C50	1,480	62.9	94.9	1.6
Cervix	C53	886	60.1	95.6	0.9
Uterine corpus	C54	244	62.7	95.9	1.6
Uterus, NOS	C55	121	60.9	52.1	29.8
Ovary	C56	288	65.2	81.9	7.3
Prostate	C61	851	73.6	91.9	2.9
Bladder	C67	626	71.4	86.6	5.0
Kidney and renal pelvis	C64–C68	292	69.0	81.2	5.5
Brain and CNS	C70–C72, D32–D33, D42–D43	285	62.1	74.4	9.8
Thyroid	C73	502	60.6	92.8	2.2
Other solid cancer		1,091	68.3	71.1	13.7
Total		22,538	68.6	76.7	9.2

[a] Cancer diagnosis made via death certificate only.

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Appendix Table D1
Fitted Cases for Alternative Radiation and Smoking Models: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

Joint effect model	Dose-response shape	Fitted cases: Baseline (nonsmoker)	Radiation only	Radiation-smoking joint effect	Smoking only	Radiation total[a]	Smoking total[b]
Males							
Multiplicative ERR	LQ[c]	7,251.7	193.5	72.9	2,954.9	266.4	3,027.8
Multiplicative ERR	L	7,187.0	251.5	96.1	2,938.5	347.6	3,034.6
Additive ERR	LQ	7,106.9	268.9	-	3,097.2	268.9	3097.2
Additive EAR	LQ	6,817.8	283.9	-	3371.3	283.9	3371.3
Unadjusted EAR	LQ	10,185.9[d]	287.1	-	-	287.1	-
Females							
Multiplicative ERR	L[c]	11,031.8	701.6	24.0	307.7	725.6	331.7
Additive ERR	L	11,012.1	727.7	-	325.2	727.7	325.2
Additive EAR	L	11054.3	718.3	-	292.4	718.3	292.4
Unadjusted EAR	L	11,325.5[d]	739.5	-	-	739.5	-

[a] Sum of radiation- and radiation-smoking-joint-effect associated cases.
[b] Sum of smoking- and radiation-smoking-joint-effect associated cases.
[c] Preferred model.
[d] Smoking cases implicitly included within baseline.

Appendix E: Sex-Specific ERR Estimates by Dose Category

Appendix table E1 presents sex-specific ERR estimates and 95% confidence intervals for each of 22 dose categories relative to the risk observed in the 0–5 Gy category for males and females with likelihood-based 95% confidence bounds. The table also includes the sampling weights for the nonparametric smoothing algorithm used in Figs. 4 and 5.

Appendix F: Effects of Updated Data and Data Subsets on Model Inference

As discussed in the main text, a number of changes with the underlying data were incorporated since the last study published in 2007 (*4*). In addition to the data accumulated since 1998, DS02 doses were revised to DS02R1 (*7*), autopsy-only cases were censored and smoking was included as an adjustment factor. As the findings, particularly regarding curvature, were different in this study compared to the last published study, we

Appendix Table E1
ERR Estimates by Dose Category and Sampling Weights Used for Smoothing: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

Dose Category (Gy)	Males: Mean dose (Gy)	ERR	SE	95% CI	Sampling weight	Females: Mean dose (Gy)	ERR	SE	95% CI	Sampling weight
0–	0	0	—	ref	59.66	0	0	—	ref	59.04
0.005–	0.01	–0.003	0.011	(<–0.01 to 0.02)	14.92	0.01	–0.002	0.017	(<–0.01 to 0.03)	14.76
0.02–	0.03	–0.005	0.017	(<–0.01 to 0.02)	6.80	0.03	0.003	0.025	(<–0.01 to 0.06)	6.53
0.04–	0.05	0.018	0.023	(<0.01 to 0.07)	3.87	0.05	0.014	0.033	(<–0.01 to 0.08))	3.98
0.06–	0.07	0.014	0.027	(<0.01 to 0.07)	2.62	0.07	0.014	0.041	(<–0.01 to 0.10)	2.52
0.08–	0.09	0.069	0.037	(0.004 to 0.15)	1.41	0.09	0.089	0.053	(<–0.01 to 0.20)	1.48
0.10–	0.11	–0.006	0.040	(<–0.01 to 0.04)	1.25	0.11	0.002	0.048	(<–0.01 to 0.10)	1.86
0.125–	0.14	–0.006	0.040	(<–0.01 to 0.04)	1.25	0.14	0.117	0.057	(0.01 to 0.24)	1.32
0.15–	0.16	0.027	0.042	(<–0.01 to 0.12)	1.11	0.16	0.235	0.073	(0.10 to 0.38)	0.80
0.175–	0.19	0.050	0.052	(<–0.01 to 0.17)	0.73	0.19	0.007	0.060	(<–0.01 to 0.14)	1.17
0.20–	0.22	–0.006	0.049	(<–0.01 to 0.08)	0.82	0.22	0.143	0.061	(0.03 to 0.27)	1.14
0.25–	0.27	0.058	0.046	(<–0.01 to 0.17)	0.94	0.28	0.164	0.065	(0.04 to 0.30)	1.01
0.30–	0.39	0.030	0.030	(<–0.01 to 0.10)	2.26	0.39	0.203	0.044	(0.12 to 0.29)	2.16
0.50–	0.61	0.052	0.039	(<0 to 0.14)	1.28	0.62	0.371	0.060	(0.26 to 0.49)	1.17
0.75–	0.86	0.319	0.069	(0.19 to 0.46)	0.42	0.86	0.559	0.090	(0.39 to 0.75)	0.52
1.00–	1.11	0.276	0.084	(0.12 to 0.46)	0.28	1.12	0.838	0.142	(0.58 to 1.13)	0.21
1.25–	1.36	0.262	0.102	(0.10 to 0.47)	0.19	1.36	0.790	0.161	(0.50 to 1.13)	0.16
1.50	1.61	0.666	0.167	(0.37 to 1.03)	0.07	1.61	1.453	0.304	(0.91 to 2.11)	0.05
1.75–	1.87	0.720	0.212	(0.35 to 1.20)	0.04	1.87	1.397	0.293	(0.87 to 2.03)	0.05
2.0–	2.26	0.670	0.166	(0.37 to 1.04)	0.07	2.27	1.533	0.278	(1.04 to 2.12)	0.05
2.5–	2.65	0.824	0.293	(0.35 to 1.46)	0.02	2.67	1.368	0.453	(0.60 to 2.39)	0.02
3.0–	3.15	1.828	1.132	(0.27 to 4.86)	0.002	3.15	0.959	1.033	(<0 to 6.07)	0.004

Notes. Excess relative risk estimates are relative to rates for the 0–5 mGy dose category. ERR estimates shown are for a person with attained age 70 after exposure at age 30. The joint effect of radiation and smoking was modeled as multiplicative.

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Appendix Table F1
Sex-Specific Linear (and Quadratic for Men) ERR Estimates and Tests for Curvature by Dose Range, Dosimetry System and Various Exclusion Criteria: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

	Male			Female	
	Dose	Dose^2	P_{curve}	Dose	P_{curve}
			DS02R1 full range		
Current analysis[a]	0.094	0.109	0.002	0.638	0.392
No smoking adjustment	0.119	0.116	0.003	0.681	0.500
Follow-up through 1998	0.088	0.090	0.018	0.618	0.217
Including autopsy-only cases	0.106	0.102	0.004	0.633	0.395
With autopsy only through 1998	0.107	0.085	0.029	0.627	0.219
Excluding high dose individuals	0.125	0.094	0.031	0.635	0.195
Excluding NIC	0.090	0.106	0.003	0.627	0.456
			DS02R1 dose range of 0–2 Gy		
Current analysis[a]	0.025	0.178	<0.001	0.635	0.073
No smoking adjustment	0.043	0.191	0.001	0.678	0.105
Follow-up through 1998	0.001	0.178	0.002	0.612	0.064
Including autopsy-only cases	0.041	0.168	0.002	0.629	0.079
With autopsy only through 1998	0.018	0.173	0.004	0.620	0.071
Excluding high dose individuals	0.036	0.182	0.001	0.631	0.072
Excluding NIC	0.023	0.174	<0.001	0.625	0.092
			DS02 full range		
Current analysis[a]	0.147	0.073	0.036	0.622	>0.5
No smoking adjustment	0.173	0.078	0.041	0.661	>0.5
Follow-up through 1998	0.138	0.061	0.099	0.604	0.283
Including autopsy-only cases	0.157	0.068	0.050	0.618	>0.5
With autopsy only through 1998	0.157	0.057	0.135	0.613	0.293
Excluding high dose individuals	0.188	0.052	0.227	0.621	0.234
Excluding NIC	0.143	0.071	0.038	0.610	>0.5
			DS02 dose range of 0–2 Gy		
Current analysis[a]	0.052	0.162	0.004	0.602	>0.5
No smoking adjustment	0.070	0.174	0.005	0.642	> 0.5
Follow-up through 1998	0.045	0.150	0.014	0.582	>0.5
Including autopsy-only cases	0.071	0.148	0.008	0.599	>0.5
With autopsy only through 1998	0.069	0.139	0.029	0.592	>0.5
Excluding high dose individuals	0.066	0.163	0.006	0.599	>0.5
Excluding NIC	0.050	0.158	0.004	0.592	>0.5

[a] Adjusted for smoking, follow-up through 2009, excluding autopsy-only cases, including high-dose survivors, including NIC.
NIC: Not in the cities of Hiroshima or Nagasaki at the time of bombing.

investigated each of these changes independently to determine if any of them were primarily responsible for the new findings of curvature. Appendix table F1 shows male ERR (linear and quadratic) and female ERR estimates (linear) along with P values for nonlinearity. The first line shows the preferred ERR model estimates; these match the estimates shown in Table 7. Main sections of the table are by dose range (full or 0–2 Gy) and by dosimetry version (DS02R1 versus the previously-used DS02). For females, no iteration shows significant evidence of curvature, although suggestive P values were observed over the range of 0–2 Gy using the updated DS02R1 doses. For males, additional follow-up and updated doses appeared to have the largest impact on curvature inference, while other factors, including adjustment for smoking, had little effect. Exclusion of the NIC group had virtually no impact on the risk estimates or curvature inferences.

Appendix G: Common and Sex-Specific Dose-Response Curvature for Selected Subsets of the Solid Cancer Cases

Appendix table G1 provides information on the sex-specific linear-quadratic fits for all solid cancers and several families of cancer subsets. These subsets are:

- Sex-specific cancers (904 males and 3,079 females) (breast, ovary, uterus and other female cancers along with prostate, testicular and other male cancers) and non-sex-specific cancers (9,569 males and 8,986 females);
- Smoking-related cancers (7,928 males and 6,016 females) (oral cavity, larynx, lung, other respiratory, esophagus, stomach, pancreas, liver, kidney, bladder and other urinary and rectum) and nonsmoking-related cancers (2,545 males and 6,049 females);
- Gastrointestinal tract (GI) cancers (6,212 males and 5,503 females) (esophagus, stomach, colon, rectum, anus, liver and pancreas) and non-GI cancers (4,261 males and 6,562 females).

Appendix table G1 includes the results for all solid cancers and for each of the subsets. Note that there was no evidence of a difference of curvature in the subset of smoking cancers only and that both males and females displayed no evidence of curvature when sex-specific cancers were analyzed. This was consistent with the data shown in Appendix table F1 (above) where removal of adjustment for smoking did not change the curvature inference for males. However, in the subset of nonsmoking cancers, only males showed evidence of curvature ($P = 0.008$ for males and $P > 0.50$ in females). The risks for smoking were not significant when the subset of nonsmoking cancers was analyzed.

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Appendix Table G1
Sex-Specific Linear-Quadratic ERR Dose-Response Model Parameter Estimates for All Solid Cancers and Various Cancer Subsets: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

	Common[a]		Sex difference[b]	Males			Females		
Outcome	Curvature	P_{curve}	P_{diff}	Linear[c]	Quadratic[d]	P_{curve}	Linear[c]	Quadratic[d]	P_{curve}
Full Range									
All solid	0.22	0.034	0.02	0.09	0.11	0.002	0.57	0.05	0.39
Sex-specific cancers only	–0.17	0.14	>0.5	0.77	–0.17	0.22	0.83	–0.13	0.22
Non-sex-specific cancers	0.51	0.001	0.02	0.03	0.13	<0.001	0.50	0.11	0.11
Nonsmoking cancers	0.16	0.18	0.02	0.21	0.26	0.008	0.59	0.01	>0.50
Smoking cancers only	0.35	0.07	0.43	0.08	0.07	0.09	0.53	0.13	0.22
Non-GI cancers	0.14	0.20	0.04	0.13	0.15	0.02	0.72	0.03	>0.50
GI cancers only	0.46	0.07	0.29	0.08	0.11	0.04	0.38	0.08	0.41
Radiation dose <2 Gy									
All solid	0.54	0.002	0.03	0.02	0.18	<0.001	0.48	0.14	0.07
Sex-specific cancers only	–0.12	0.48	>0.5	0.74	–0.13	>0.5	0.79	–0.08	>0.5
Non-sex-specific cancers	1.2	<0.001	>0.5	–0.02	0.19	<0.001	0.38	0.23	0.01
Nonsmoking cancers	0.31	0.09	0.05	0.11	0.35	0.01	0.54	0.05	>0.5
Smoking cancers only	1.06	0.005	0.39	0.02	0.14	0.04	0.38	0.28	0.04
Non-GI cancers	0.50	0.008	0.19	–0.01	0.31	<0.001	0.63	0.12	0.24
GI cancers only	0.71	0.08	>0.5	0.09	0.09	0.27	0.28	0.18	0.16

[a] Quadratic-to-linear coefficient ratio in an ERR dose-response model that allows the linear coefficient to depend on sex but constrains the curvature to be equal for males and females.
[b] P value of a test of the hypothesis of equal curvature in males and females.
[c] Linear dose coefficient in a linear-quadratic ERR model with dose in units of weighted colon dose in Gy.
[d] Quadratic dose coefficient in a linear-quadratic ERR model with dose in units of weighted colon dose in Gy.

Non-sex-specific cancers. Differences in sex-specific curvature were pronounced for the sex-specific vs. non-sex-specific cancer groups shown in appendix table G1. There was no indication of curvature among sex-specific cancers ($P > 0.5$) for either males ($P = 0.22$) or females ($P = 0.22$). However, for non-sex-specific cancers (i.e., cancers that occur in both men and women) as a group, there was a strong indication of upward curvature ($P = 0.02$) that appeared to be largely driven by the male dose response ($P < 0.001$) with a suggestion of upward curvature for women ($P = 0.11$).

Appendix table G2 provides more detail on the ERR and EAR dose-response estimates for non-sex-specific cancers in males and females as well as point estimates of the risks at 1 Gy and 0.1 Gy (after exposure at age 30 years with attained age of 70 years). The evidence of upward curvature in the dose response for both males and females is stronger when focus is placed on the 0–2 Gy dose range. Over the restricted 0–2 Gy dose range, there is evidence of curvature among females in both the ERR and EAR models.

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Appendix Table G2
ERR and EAR Dose-Response Model Parameter Estimates for Non-Sex-Specific Solid Cancers by Sex Using all Doses and the 0–2 Gy Dose Range: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

Model (dose range)	Linear (95% CI)	Quadratic (95% CI)	Curvature P value	Risk at 1 Gy (95% CI)[a]	Risk at 0.1 Gy (95% CI)[a]
Male					
ERR (all doses)	0.027 (<–0.03 to 0.10)	0.13 (0.06 to 0.22)	<0.001	0.16 (0.08 to 0.23)	0.004 (–0.005 to 0.01)
ERR (0–2 Gy)	–0.023 (<–0.03 to 0.11)	0.18 (0.09 to >0.25)	<0.001	0.16 (0.09 to 0.23)	–0.0004 (–0.01 to 0.01)
EAR (all doses)	6.1 (–14 to 29)	25.7 (12 to 42)	<0.001	31.8 (18 to 45)	0.86 (–0.96 to 2.7)
EAR (0–2 Gy)	–4.2 (<–17 to 21)	36.3 (17 to 58)	<0.001	32.1 (19 to 45)	–0.06 (–2.0 to 1.9)
Female					
ERR (all doses)	0.50 (0.29 to 0.73)	0.11 (–0.02 to 0.26)	0.11	0.61 (0.47 to 0.75)	0.051 (0.03 to 0.07)
ERR (0–2 Gy)	0.38 (0.16 to 0.63)	0.23 (0.04 to 0.42)	0.01	0.61 (0.47 to 0.76)	0.04 (0.02 to 0.06)
EAR (all doses)	31.3 (18 to 46)	7.3 (–1.5 to 17)	0.11	38.7 (29.6 to 47.7)	3.2 (1.9 to 4.8)
EAR (0–2 Gy)	24.0 (10 to 40)	14.9 (3.0 to 28)	0.01	38.9 (30 to 48)	2.5 (1.2 to 4.0)

[a] Wald bounds.

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