Effect of Heterogeneity in Background Incidence on Inference About the Solid-cancer Radiation Dose Response in Atomic-bomb Survivors

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SUPPLEMENTARY INFORMATION

1. Computation of confidence region for the curvature-parameter estimate

Let β be the linear coefficient and γ the quadratic coefficient in a linear-quadratic model for the excess relative risk for radiation — i.e., ERR = $\beta d + \gamma d^2$. The curvature is defined by the model $\beta(d + \theta d^2)$, where $\theta = \gamma/\beta$. This model is fit in Epicure by specifying sex in the product-linear (PLINEAR) subcommand in a model definition statement (in reality, all of these parameters are sex-specific; we ignore this for simplicity of presentation).

Because θ is a function of two parameters, to obtain a confidence region for θ requires that we consider a region based jointly on β and γ, which is typically not straightforward to derive. An ordinary confidence interval computed directly for θ could be used, but is not appropriate when the estimate of β is not statistically significant, because then the confidence interval for β includes zero and thus θ could be infinite because β is the denominator. In constructing a confidence region for θ we therefore have to account for this division by zero. The value of θ approaches infinity as β approaches zero, but whether θ approaches positive infinity or negative infinity depends on whether β approaches zero from the right (positive values of β) or from the left (negative values of β). So we have to consider two separate parts of a confidence region for θ: one corresponding to negative values of β and the other corresponding to positive values of β. With the former the maximum is attained as β approaches its lower (negative) confidence bound, and with the latter the minimum is attained as β approaches its upper (positive) confidence bound. Thus, assuming that the quadratic coefficient γ is significantly different from zero, we have the confidence region

$$(-\infty, \theta^-) \cup (\theta^+, +\infty) \qquad \text{(S1)}$$

where "∪" denotes the union of the two intervals. This type of confidence region is not the typical type of confidence interval ordinarily reported in standard regression programs. However, if the quadratic coefficient γ is significantly different from zero (i.e., the confidence interval for γ does not include zero), we can invert θ — i.e., $\theta^{-1} = \beta/\gamma$ in the model $\gamma(\theta^{-1}d + d^2)$ — and calculate bounds for

the inverse of the curvature, θ^{-1}, using the standard approach to computing a confidence interval, because there is no division by zero. The lower bound for θ^{-1} provides the inverse of the upper bound θ^{-} of the lower confidence region for θ in (S1), and the upper bound for θ^{-1} provides the lower bound θ^{+} of the upper confidence region for θ in (S1). To simplify reporting results, we denote this confidence region by "] θ^{-}, θ^{+} [" to signify the range of values that are outside the confidence region (i.e., the values between θ^{-} and θ^{+} are not part of the confidence region).

Note that when the quadratic coefficient γ is not significantly different from zero, the difficulty of division by zero arises with the inverse of the curvature. In that case, if β is significantly different from zero, we can use the ordinary bounds for θ. Otherwise (i.e. both the linear and quadratic coefficient estimates are not significantly different from zero), there is no specific confidence region for θ or θ^{-1} as both can involve division by zero, and so any value of θ in $(-\infty, \infty)$ is consistent with the data.

2. Complete results with individual-site exclusion: males

Table S1 presents a complete list of cancer sites in the LSS solid cancer incidence study and the impact of removing them individually — by censoring — on the estimated curvature in the male radiation dose response for all remaining solid cancers as a group. This analysis was performed with the dose response for females set to be linear, as described in the main report. Table S2 shows analogous results from fits restricted to LSS males (with females excluded). With exclusion of some of the most-influential sites, the confidence region for the curvature parameter was non-informative — $(-\infty, +\infty)$ — generally because the quadratic coefficient was not significantly different from zero and the likelihood-ratio test P value for the linear coefficient was close to 0.05; in such scenarios, we do not report the P value for a test of the curvature parameter.

Supplementary Table S1. Estimated curvature of radiation ERR dose response among males with exclusion of individual cancer sites (using data from all LSS participants)

Site(s) excluded	ERR curvature parameter among males			Number of cases excluded		
	Curvature estimate	95% confidence limits	P value	Total	Male	Female
None	1.16	] –8.40, 0.18 [[a]	0.0024	0	0	0
Solid cancer sites with cases among males						
Brain/CNS (including benign)	0.89	] –16.9, 0.11 [	0.0091	285	99	186
Esophagus	0.89	] –26.5, 0.12 [	0.0066	486	394	92
Thyroid	0.90	] –14.9, 0.12 [	0.0073	502	72	430
Bone/connective	0.90	] –31.0, 0.12 [	0.0062	72	34	38
Non-melanoma skin cancer	0.96	] –8.90, 0.11 [	0.0090	516	195	321
Kidney	0.98	] –17.6, 0.15 [	0.0041	292	158	134
Gall bladder	1.03	] –13.1, 0.16 [	0.0035	354	84	270
Pancreas	1.04	] –12.0, 0.16 [	0.0035	723	306	417
Stomach	1.07	] –9.66, 0.14 [	0.0061	5,661	3,090	2,571
Other solid cancers	1.10	] –9.48, 0.17 [	0.0033	325	122	203
Other biliary	1.11	] –9.35, 0.17 [	0.0028	340	136	204
Larynx	1.11	] –10.0, 0.17 [	0.0028	180	154	26
Intra-hepatic biliary duct	1.16	] –8.31, 0.18 [	0.0026	131	44	87
Melanoma	1.16	] –8.46, 0.18 [	0.0024	22	10	12
Male breast	1.18	] –7.74, 0.18 [	0.0025	10	10	0
Other urinary	1.19	] –7.30, 0.18 [	0.0026	90	42	48
Other digestive	1.19	] –7.79, 0.19 [	0.0023	79	26	53

Rectum	1.23	] –7.97, 0.20 [	0.0017	1.046	518	528
Lung	1.25	] –6.76, 0.19 [	0.0024	2,446	1,445	1,001
Other respiratory	1.26	] –6.83, 0.20 [	0.0019	115	52	63
Other endocrine	1.27	] –6.52, 0.20 [	0.0019	71	37	34
Colon	1.31	] –5.21, 0.18 [	0.0033	1,914	782	1,132
Other male cancers	1.36	] –5.82, 0.22 [	0.0015	43	43	0
Bladder	1.37	] –5.87, 0.22 [	0.0015	626	411	215
Oral	1.49	] –4.78, 0.23 [	0.0013	394	236	158
Liver	1.67	] –3.89, 0.24 [	0.0015	1,885	1,122	763
Prostate	1.99	] –3.64, 0.29 [	<0.001	851	851	0
		Female-specific cancers				
Uterine corpus	1.12	] –9.01, 0.18 [	0.0028	244	0	244
Other female cancers	1.14	] –8.98, 0.18 [	0.0026	70	0	70
Ovary	1.15	] –8.64, 0.18 [	0.0026	288	0	288
Uterine NOS	1.15	] –8.57, 0.18 [	0.0025	121	0	121
Cervix	1.27	] –6.93, 0.21 [	0.0018	886	0	886
Breast	1.29	] –6.72, 0.20 [	0.0019	1,470	0	1,470

[a] The notation "] , [" connotes a two-part confidence region for the curvature-parameter estimate in scenarios where the linear coefficient was not statistically significant (i.e., a value of zero for the linear coefficient, which induces infinite curvature, is compatible with the data). The region includes all values of the curvature parameter outside the limits; values between the limits are not consistent with the data.

Supplementary Table S2. Estimated curvature of radiation ERR dose response among males with exclusion of individual cancer sites (using data from only male LSS participants)

Site(s) excluded	ERR curvature parameter among males			Number of cases excluded
	Curvature estimate	95% confidence region or limits	P value	
None	1.16	] –8.40, 0.18 [[a]	0.0024	0
Esophagus	0.61	(–∞, +∞)		394
Thyroid	0.63	(–∞, +∞)		72
Brain/CNS	0.64	(–∞, +∞)		99
Bone/connective	0.65	(0.007, 39.0)	0.046	34
Non-melanoma skin cancer	0.67	(–∞, +∞)		195
Kidney	0.70	(0.027, 136)	0.034	158
Gall bladder	0.75	] –43.9, 0.033 [	0.031	84
Pancreas	0.79	] –22.0, 0.044 [	0.027	306
Colon	0.81	] –9.17, 0.012 [	0.043	782
Other biliary	0.81	] –17.4, 0.046 [	0.026	136
Other solid cancers	0.83	] –15.8, 0.050 [	0.025	122
Larynx	0.83	] –19.5, 0.056 [	0.023	154
Intra-hepatic biliary duct	0.84	] –14.3, 0.052 [	0.024	44
Melanoma	0.84	] –15.1, 0.055 [	0.023	10
Other urinary	0.85	] –11.8, 0.049 [	0.026	42
Rectum	0.86	] –16.5, 0.066 [	0.020	518
Lung	0.87	] –12.0, 0.056 [	0.023	1,445
Other digestive	0.87	] –12.6, 0.058 [	0.022	26
Male breast	0.89	] –11.2, 0.065 [	0.020	10
Other respiratory	0.90	] –10.5, 0.067 [	0.020	52
Other endocrine	0.91	] –9.69, 0.067 [	0.020	37
Bladder	0.96	] –8.68, 0.076 [	0.018	411
Other male cancers	1.01	] –7.60, 0.087 [	0.015	43
Oral	1.05	] –6.04, 0.088 [	0.015	236
Liver	1.08	] –4.81, 0.062 [	0.023	1,122
Stomach	1.33	] –5.38, 0.15 [	0.007	3,090
Prostate	1.38	] –4.22, 0.13 [	0.010	851

[a] The notation "] , [" connotes a two-part confidence region for the curvature-parameter estimate in scenarios where the linear coefficient was not statistically significant (i.e., a value of zero for the linear coefficient, which induces infinite curvature, is compatible with the data). The region includes all values of the curvature parameter outside the limits; values between the limits are not consistent with the data. The notation "(,)" denotes the usual confidence interval.

By comparing results in Table S2 with those in Table 1 of the main report, we see that in the male subset of the LSS the evidence for curvature is weaker than when the full LSS is analyzed. In other words, excluding women from the data under analysis substantially diminishes the evidence for curvature in the dose response among males. As noted in the main report, some of the background-rate parameters in the analysis based on the full LSS data are not sex-specific, so females will contribute to the intercept (background incidence) for males.

3. Complete results with individual-site exclusion: females

Table S3 presents a complete list of cancer sites in the LSS solid cancer incidence study and the effect of removing them individually — by censoring — on the estimated curvature in the female radiation dose response for all remaining solid cancers as a group. This analysis was performed with the dose response for males set to be linear-quadratic (by using the curvature parameter defined previously). With no individual site did exclusion result in a likelihood-ratio test P value for the linear coefficient that was 0.05 or larger, so the standard 95% likelihood-based confidence interval for the curvature parameter could be computed in all scenarios.

Supplementary Table S3. Estimated curvature of radiation ERR dose response among females with exclusion of individual cancer sites (using data from all LSS participants)

Site(s) excluded	ERR curvature parameter among females			Number of cases excluded		
	Curvature estimate	95% confidence region [a]	P value	Total	Male	Female
None	0.085	(–0.085, 0.39)	0.39	0	0	0
Solid cancer sites with cases among females						
Breast	0.27	(–0.022, 1.03)	0.080	1,470	0	1,470
Stomach	0.16	(–0.051, 0.56)	0.17	5,661	3,090	2,571
Thyroid	0.14	(–0.068, 0.55)	0.24	502	72	430
Pancreas	0.097	(–0.078, 0.41)	0.34	723	306	417
Uterine NOS	0.096	(–0.078, 0.41)	0.34	121	0	121
Bladder	0.094	(–0.082, 0.41)	0.36	626	411	215
Other endocrine	0.092	(–0.081, 0.40)	0.36	71	37	34
Larynx	0.085	(–0.084, 0.38)	0.39	180	154	26
Other female cancers	0.085	(–0.084, 0.39)	0.39	70	0	70
Lung	0.085	(–0.092, 0.41)	0.42	2,446	1,445	1,001
Melanoma	0.084	(–0.086, 0.38)	0.40	22	10	12
Other solid cancers	0.084	(–0.087, 0.39)	0.40	325	122	203
Brain/CNS (including benign)	0.082	(–0.087, 0.38)	0.41	285	99	186

Other respiratory	0.080	(–0.088, 0.38)	0.42	115	52	63
Other digestive	0.080	(–0.089, 0.38)	0.42	79	26	53
Cervix	0.078	(–0.087, 0.36)	0.42	886	0	886
Esophagus	0.077	(–0.090, 0.37)	0.43	486	394	92
Non-melanoma skin cancer	0.077	(–0.094, 0.39)	0.45	516	195	321
Other biliary	0.076	(–0.090, 0.37)	0.44	340	136	204
Bone/connective	0.075	(–0.091, 0.37)	0.44	72	34	38
Kidney	0.075	(–0.092, 0.37)	0.45	292	158	134
Gall bladder	0.074	(–0.090, 0.36)	0.44	354	84	270
Ovary	0.070	(–0.093, 0.36)	0.47	288	0	288
Other urinary	0.069	(–0.096, 0.36)	0.48	90	42	48
Uterine corpus	0.068	(–0.095, 0.35)	0.49	244	0	244
Intra-hepatic biliary duct	0.064	(–0.098, 0.35)	>0.5	131	44	87
Colon	0.064	(–0.10, 0.36)	>0.5	1,914	782	1,132
Oral	0.063	(–0.10, 0.35)	>0.5	394	236	158
Rectum	0.052	(–0.10, 0.33)	>0.5	1.046	518	528
Liver	0.044	(–0.11, 0.32)	>0.5	1,885	1,122	763
		Male-specific cancers				
Male breast	0.090	(–0.082, 0.40)	0.37	10	10	0

Prostate	0.088	(–0.084, 0.39)	0.38	851	851	0
Other male cancers	0.086	(–0.084, 0.39)	0.39	43	43	0

[a] The linear coefficient of the dose response for females was statistically significant in all scenarios with removal of one site at a time; therefore, the ordinary 95% likelihood based confidence interval is reported in each row.

Table S4. Estimated curvature of radiation dose response among females with exclusion of increasingly larger groups of the most influential cancer sites (using data from all LSS participants)

Sites excluded by censoring	ERR curvature parameter among females			Number of cases excluded	
	Curvature estimate	95% confidence region or limits	P value	Male	Female
None	0.085	(–0.085, 0.39)	0.39	0	0
Breast and stomach	0.54	(0.066, 2.49) [a]	0.015	3,090	4,041
Breast, stomach, and thyroid	1.29	] –9.30, 0.20 [[b]	0.0027	3,162	4,471

[a] With removal of both breast and stomach cancers, the estimated curvature in the female dose response increased and became statistically significant, but the linear term was still significant, so the ordinary confidence interval could be used.

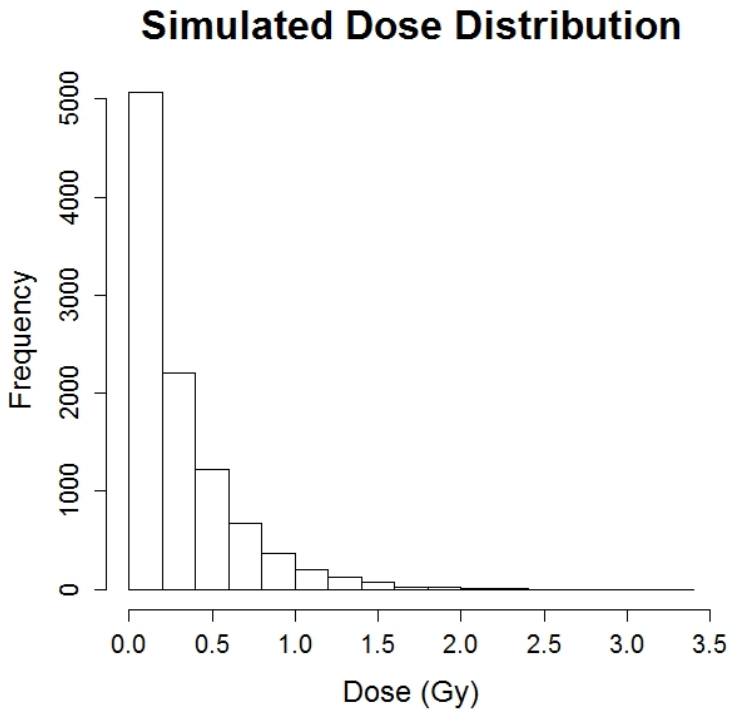
[b] With the combination of breast, stomach, and thyroid cancers removed, the estimated curvature in the female dose response was even higher and the linear term became non-significant; hence, the two-part confidence region based on the inverse curvature parameter is reported.

4. Hypothetical example to illustrate how the intercept influences the dose response

Here we present a simple simulated example that demonstrates the effect that a small change in the intercept of the dose-response (i.e. a bias in the background rates) can have on inference about curvature in the dose response. To focus on how the dose-response intercept is in fact a reflection of the estimated background rates, we fit the dose response on the incidence scale rather than on the relative risk scale.

For this example, we simulate a slightly zero-inflated exponential dose distribution and Poisson distributed outcomes that are similar in magnitude to the all solid cancer incidence, with a linear dose response that assumes a rate ratio of 1.5 at 1 Gy. To make the example simple, we ignore effects of age, time, and other covariates in the background model and we perform simple linear regression. We also assume that every person-year-cell observation has the same weight, but given that the simulated data mimic the true data, the results reflect what was seen in the analyses of the main report. The example is run with the statistical analysis software R: text on a line following the pound sign ("#") is explanatory text ("comments", not program code). Plotting commands used to generate the figures in this example have been removed to keep the code simple. Elements of the R example (program code, comments, and output) are shown in `courier font type in the color purple`. Comments and program code are shown in **`bold courier font (COMMENTS IN ALL CAPITAL LETTERS)`**; output is shown in `regular (non-bold) courier font`.

```
# BACKGROUND INTERCEPT
   a1 <- exp(-5)*10000
# ERR .5
   b <- .5*a1

# GENERATE THE SIMULATED DOSES (1000 ZEROES, 9000 EXPONENTIAL VALUES)
   d <- c(rep(0,1000), rexp(9000,3))

# DRAW A HISTOGRAM OF THE SIMULATED DOSES
```



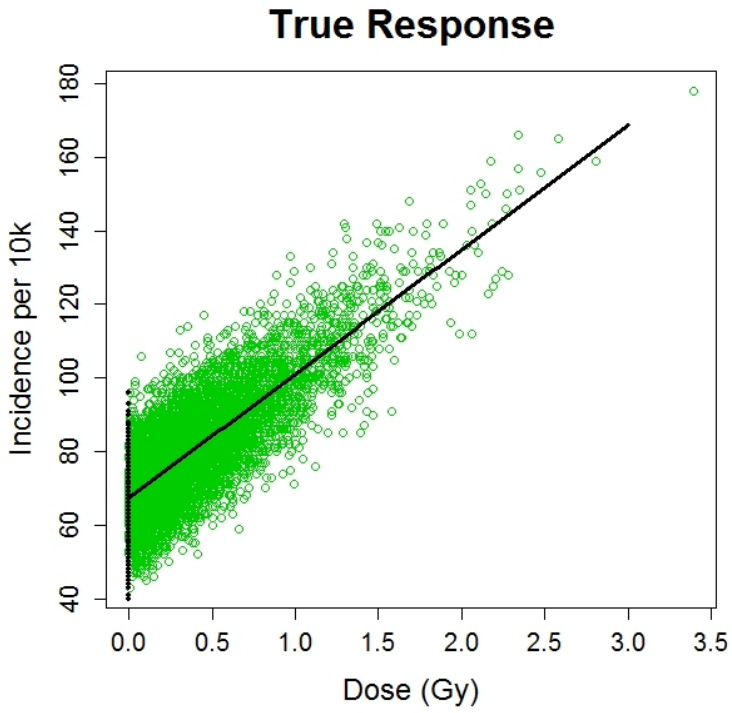

```
# TRUE MODEL
    lambda1 <- a1 + b*d

# GENERATE THE POISSON RESPONSE ACCORDING TO THE TRUE MODEL
    y1 <- rpois(length(d), lambda1)

# FIT A REGRESSION TO THE "TRUE" DATA (DATA GENERATED BY THE TRUE MODEL)
    summary(lm(y1 ~ d))

    Call:
    lm(formula = y1 ~ d)

    Residuals:
        Min      1Q  Median      3Q     Max
    -30.623  -6.003  -0.094   5.777  36.009

    Coefficients:
```

```
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  67.3824     0.1193   564.7   <2e-16 ***
d            33.7750     0.2655   127.2   <2e-16 ***
---
Residual standard error: 8.842 on 9998 degrees of freedom
Multiple R-squared:  0.6181,    Adjusted R-squared:  0.6181
F-statistic: 1.618e+04 on 1 and 9998 DF,  p-value: < 2.2e-16
```

Note that the linear coefficient estimate (estimated slope, 33.8) is about half as large as the background parameter (intercept, 67.4), giving an ERR estimate of about 0.50 per Gy, as expected.

```
# ADD THE SQUARE OF DOSE (QUADRATIC TERM) TO FIT A LINEAR-QUADRATIC MODEL
d2 <- d*d
summary(lm(y1 ~ d + d2))

Call:
lm(formula = y1 ~ d + d2)

Residuals:
    Min      1Q  Median      3Q     Max
-30.621  -6.003  -0.093   5.777  36.008

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) 67.383571   0.140642 479.115   <2e-16 ***
d           33.766470   0.584914  57.729   <2e-16 ***
d2           0.006679   0.410132   0.016    0.987
---
Residual standard error: 8.842 on 9997 degrees of freedom
Multiple R-squared:  0.6181,    Adjusted R-squared:  0.618
F-statistic:  8091 on 2 and 9997 DF,  p-value: < 2.2e-16
```

Following is a plot of the data with the fitted regression lines. The values of the outcome at zero dose are shown with black points; all other outcome values are shown with green points.

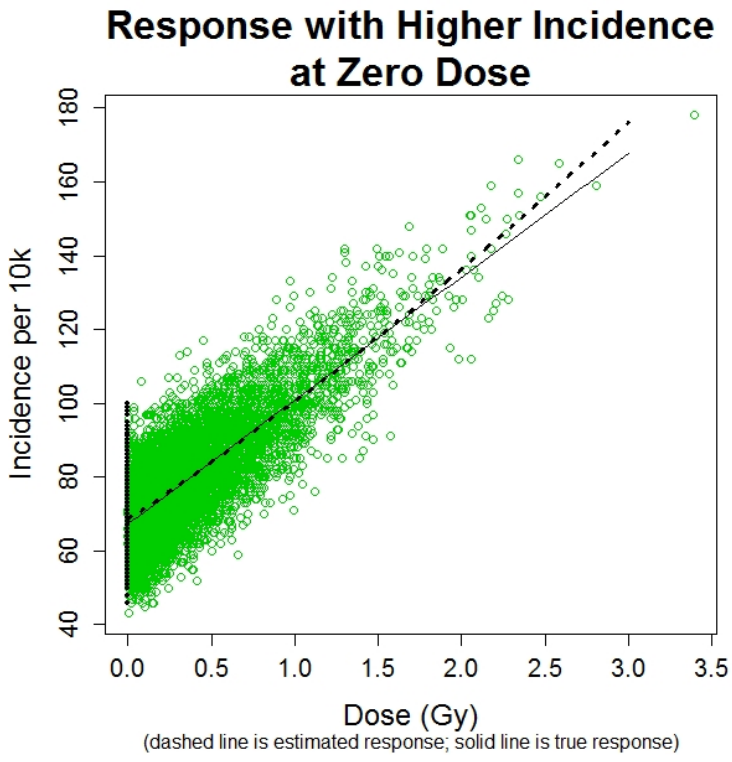


The quadratic coefficient estimate (0.0067) is indistinguishable from zero, and the linear coefficient estimate (about 33.8) has not changed appreciably. The fitted linear model is shown as the solid line in the plot below; the fitted linear-quadratic model (plotted as a dashed line) cannot be distinguished from the linear fit.

```
# NOW ADD A SMALL INCREMENT TO THE BACKGROUND RATE, TO MIMIC
#   WHAT MIGHT HAPPEN IF THERE WERE A BIAS IN THE INTERCEPT
    y2 <- y1
    a2 <- exp(-4.925)*10000
    y2[d==0] <- rpois(length(d[d==0]), a2)

# FIT A LINEAR-QUADRATIC MODEL TO THE BACKGROUND-PERTURBED DATA
    summary(lm(y2 ~ d + d2))

    Call:
```

```
lm(formula = y2 ~ d + d2)

Residuals:
    Min      1Q  Median      3Q     Max
-30.194  -6.117  -0.180   5.941  35.008

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  68.6746     0.1433 479.377  < 2e-16 ***
d            29.8457     0.5958  50.094  < 2e-16 ***
d2            1.9994     0.4178   4.786 1.73e-06 ***
---
Residual standard error: 9.007 on 9997 degrees of freedom
Multiple R-squared:  0.5896,    Adjusted R-squared:  0.5895
F-statistic:  7181 on 2 and 9997 DF,  p-value: < 2.2e-16
```

Following is a plot of the data and fitted dose response with the background-perturbed data.



The linear-quadratic fit to the background-perturbed data is shown as a dashed line. For comparison, the linear fit to the true data is shown as a solid line. Note that the overall distribution of values at zero dose is only slightly higher than it was in the previous plot. Nevertheless, because of the relatively large number of observations at zero dose (vis-à-vis the relatively small number of observations at higher doses), the quadratic coefficient estimate (2.00) is quite different from zero (and positive). Note also that the linear coefficient estimate (29.8) has decreased somewhat from its true value of 33.8. In other words, introducing a small bias in the intercept of the dose response (the background rates) resulted in spurious curvature in the dose response.

5. Parameter estimates obtained with the joint model

Supplementary table S5 shows the fitted background-rate parameters for the joint model with groups M and O, using the same parametric background model as was originally used by Grant et al (reference (*1*) in the main manuscript). The fitted background-rate models in age are illustrated in Figure 2 of the main text. The estimated quadratic age coefficients for group M changed sign from negative to positive; we attribute this to need to fit the higher incidence at young ages. In addition, the estimated coefficients of the age-spline terms at ages above 70 for group M became dramatically more negative, presumably to accommodate the leveling-off of the rate at higher ages that could not be fit adequately when the quadratic term became positive. The coefficient for birth year was close to 50% greater in the M group than in the O group. In other words, the background-rate model for group M differs substantially from that for all solid cancer as a single outcome, and therefore is not adequately fit by a single, common background-rate model for all solid cancer.

Supplementary Table S5. Estimated coefficients for two cancer-site groups based on joint analysis of all LSS members with fully heterogeneous parametric background-rate model

Variable	Cancer-site group	
	M: thyroid, brain/CNS, and bone/connective	**O: all other solid cancer**
Male intercept [a]	1.31	4.88
Male log([attained age] / 70) (linear)	4.26	4.91
Male $\{\log([\text{attained age}] / 70)\}^2$ (quadratic)	1.64	–1.09
Male $\log\{([\text{attained age}] / 70)\}^2$ if attained age > 70 yr (0 otherwise; quadratic spline)	–16.4	–9.31
Male birth year	0.195	0.136
Female intercept [a]	1.51	4.42
Female log([attained age] / 70) (linear)	2.78	3.45
Female $\{\log([\text{attained age}] / 70)\}^2$ (quadratic)	0.288	–0.020
Female $\log\{([\text{attained age}] / 70)\}^2$ if attained age > 70 yr (0 otherwise; quadratic spline)	–16.9	–3.07
Female birth year	0.291	0.053
Hiroshima-NIC interaction [b]	–0.266	–0.028
Nagasaki-NIC interaction [b]	–0.681	–0.081

[a] log incidence per 10^5 persons per year among non-exposed people aged 70, who were born in 1915, who had never smoked, and who were in either city at the time of the bombing

[b] Parameter not sex-specific

6. Explanation of dose-error adjustment for the quadratic dose-response parameter

It might not be widely understood that, when the square of dose is incorporated in the dose-response model with the LSS data, a further adjustment is required beyond that built into the error-corrected DS02R1 dose estimates. This is because the DS02R1 radiation dose estimates used in LSS analyses are adjusted to correct for measurement error based on a linear regression-calibration model for measurement-error adjustment. The theoretical basis for this is provided in a technical report by Pierce and others (*7*). Table 4 of that technical report provides estimates of the squared coefficient of variation of the replacement term for the linear term in the dose response. Based on the usual definition of variance ($v(X|Z) = E(X^2|Z) - [E(X|Z)]^2$), Pierce and others (*7*) noted that the estimated replacement value for the quadratic term can be obtained by adding 1.0 to the squared coefficient of variation of the linear replacement term. The rather small variation among values in their Table 4, coupled with the inferred error on the log scale of about 35% (*2*), produces an approximate value of $1.12 \times [E(X|Z)]^2$ for the quadratic term when adding dose-squared to the dose-response model, where $E(X|Z)$ is the bias-corrected linear radiation-dose term. Therefore, when adding a quadratic parameter to the radiation dose response, the adjusted dose estimate is squared and then multiplied by 1.12.