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Effect of Heterogeneity in Background Incidence on Inference about the Solid-Cancer Radiation Dose Response in Atomic Bomb Survivors

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A recent analysis of solid cancer incidence in the Life Span Study of atomic bomb survivors (Hiroshima and Nagasaki, Japan) found evidence of a nonlinear, upwardly curving radiation dose response among males but not among females. Further analysis of this new and unexpected finding was necessary. We used two approaches to investigate this finding. In one approach, we excluded individual cancer sites or groups of sites from all solid cancers. In the other approach, we used joint analysis to allow for heterogeneity in background-rate parameters across groups of cancers with dissimilar trends in background rates. Exclusion of a few sites led to the disappearance of curvature among males in the remaining collection of solid cancers; some of these influential sites have unique features in their background age-specific incidence that are not captured by a background-rate model fit to all solid cancers combined. Exclusion of a few sites also led to an appearance of curvature among females. Misspecification of background rates can cause bias in inference about the shape of the dose response, so heterogeneity of background rates might explain at least part of the all solid cancer dose-response difference in curvature between males and females. We conclude that analysis based on all solid cancers as a single outcome is not the optimal method to assess radiation risk for solid cancer in the Life Span Study; joint analysis with suitable choices of cancer groups might be preferable by allowing for background-rate heterogeneity across sites while providing greater power to assess radiation risk than analyses of individual sites.

INTRODUCTION

The Radiation Effects Research Foundation has been conducting studies on health effects of atomic bomb radiation among survivors of the bombings in Hiroshima and Nagasaki with follow-up for incident cancer in the Life Span Study (LSS) since 1958. The recently published finding by Grant *et al*. (*1*) of nonlinearity (upward curvature) in the radiation dose response for all solid cancer incidences among male, but not female, survivors is new and intriguing. However, this difference is unexpected and difficult to interpret; thus, it requires further investigation.

Grant *et al*. (*1*) ruled out several possible explanations. They assessed effects of smoking adjustment and the non-exposed sub-cohort of not-in-city residents. They assessed whether the difference was due to the revised DS02R1 radiation doses (*2*) and tested the curvature using a restricted dose range (0–2 Gy). They also assessed whether the difference was related to sex-specific versus non-sex-specific cancers, smoking-related versus non-smoking-related cancers, gastrointestinal (GI) tract versus non-GI tract cancers, or adjustment for survivors whose unshielded kerma doses were above 4 Gy (and possibly subject to greater dose-estimation error). None of these analyses definitively revealed the source of curvature among males, although the change in dosimetry was the most influential among the causes considered. Noting that their results raised ''unresolved questions'' [(*1*); p. 513], they concluded, ''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'' [(*1*); see p. 528]. It seems unlikely that a sex-specific difference in curvature in the dose response is a hallmark of all solid cancers. It is therefore important to understand the source of the observed curvature difference because, at low doses, spurious estimated curvature (if positive) would lead to underestimation of risk, whereas lack of estimated curvature (if indeed curvature exists)

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would lead to overestimation of risk. In this work, it is not our intention to answer the questions raised by the results of Grant *et al*. (*1*); rather, our goal was to determine whether there might be a simple explanation for the sex-specific difference in curvature and, if so, whether questions about dose-response shape can be better addressed with alternatives to conventional analyses of all solid cancer.

In addition to heterogeneity in the shape of the dose response, one should also consider heterogeneity in background rates, which are the incidence rates in the absence of radiation exposure. With analyses of all solid cancers, a single background-rate model is applied to all organs (sites of cancer) simultaneously, but background rates of cancer are well known to vary widely according to cancer site in regard to age, period, birth-cohort effects and other factors. Fitted background rates can affect the shape and magnitude of the dose response (*3*, *4*), so that lack of adequate background-rate adjustment could result in biased inference about the dose response and therefore might partly explain the observed male-female difference in dose-response curvature. A simple example of this phenomenon is provided in the Supplementary Information (http://dx.doi.org/10.1667/RR15127.1.S1).

Individual cancer site-specific analyses can be used to assess dose-response curvature, but they could suffer from lack of power due to small numbers of radiation-associated cases and could be subject to bias from informative or dependent censoring (ignoring the large number of other solid cancers). In the current work we therefore used two approaches based on all solid cancers: 1. We excluded individual sites of cancer one-by-one; 2. We conducted a joint analysis based on groups of cancer sites. Our goal was to further understand the source of the sex-specific difference in curvature for all solid cancers combined and to ascertain whether heterogeneity in background rates might contribute to it. It was not our intention to elucidate which individual sites of cancer might demonstrate curvature in the radiation dose response; that is for more focused analyses, such as site-specific analyses, to determine (and many are underway; see Discussion for examples). Grant *et al*. (*1*) reported curvature in the dose response for males with both an excess relative risk (ERR) and an excess absolute rate (EAR) model. We focus here on the ERR dose-response model, since the two models are merely alternative algebraic representations of the same total incidence.

METHODS

Study Cohort

The LSS is a cohort study of 120,321 persons who were atomic bomb survivors or other (not in either city [NIC] at the times the bombs were exploded) residents of Hiroshima and Nagasaki, Japan. The cohort was defined from information obtained in censuses taken in 1950 and after, and nearly complete mortality follow-up has been conducted since then (*5*). Several mail surveys have provided information on lifestyle factors such as smoking. Radiation doses have been estimated through dose reconstruction work that is unusually precise and complete for a large retrospective cohort study (*2*). Follow-up of the cohort with regard to solid cancer incidence began in 1958 and is based on local cancer registries in Hiroshima and Nagasaki prefectures. Analyses herein are restricted to the sub-cohort with known radiation dose estimates (105,444 individuals, including 25,239 NIC LSS members who are assigned doses of zero). Analyses include adjustment for estimated rates of migration out of the registry catchment areas as explained by Grant *et al*. (*1*). As of the end of 2009, a total of 22,538 cases of first primary solid cancer, excluding *in situ* tumors and cases ascertained by autopsy only, had occurred (10,473 among males, 12,065 among females) during 3.079×10^6 person-years of follow-up (1.142×10^6 among males, 1.937×10^6 among females), producing an overall crude (not age- or sex-specific) solid cancer incidence of 73.2 per 10^5 persons per year.

The LSS cohort study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation. Approval to link to cohort members' data from cancer registries was provided by Hiroshima and Nagasaki Prefectures and the City of Hiroshima.

Estimation of Radiation Effects

Incidence of solid cancer and ERR for radiation were estimated from highly-stratified person-year data and a Poisson regression model for the background cancer incidence and the excess risk, with adjustment for smoking behavior, as explained in detail elsewhere (*1*). We briefly explain the estimation of ERR here. The linear-quadratic model for the ERR has the form $[1 + (\beta_s d + \gamma_s d_*^2) \times e^{\delta_1 a + \delta_2 e + \delta_3 I_{4Gy}}]$, where d is radiation dose (Gy) adjusted for random measurement error (*6*), d_*^2 is the square of estimated dose with an additional adjustment for nonlinearity in the dose-error correction (*7*) (see Supplementary Information for further details; http://dx.doi.org/10.1667/RR15127.1.S1), β_s is a sex-specific linear coefficient of dose, γ_s is a sex-specific quadratic coefficient of dose (coefficient of dose squared), and $e^{\delta_1 a + \delta_2 e + \delta_3 I_{4Gy}}$ is the risk-modification function of log of attained age [centered at 70 years; i.e., $a = \log(\{\text{attained age}\}/70)$], age at exposure (centered at 30 years; i.e., $e = \{\text{age at exposure}\} - 30$), and being exposed to total unshielded (free-in-air) kerma in excess of 4 Gy (I_{4Gy} is an indicator function with value 1 if kerma exceeds 4 Gy and 0 otherwise). We followed the usual convention of using dose to the colon, as a surrogate for all organ doses, with a constant neutron weight of ten.

Assuming linearity in the female dose response as reported by Grant *et al*. (*1*) and ignoring the effect-modifying term for simplicity, we can rewrite the ERR as $[1 + (\beta_s d + \gamma_M d_*^2)]$ where γ_M is the quadratic coefficient among males. To focus on the curvature among males, we separate the male and female linear coefficients, $\beta_s d = \beta_F d + \beta_M d$, with each coefficient defined to be zero for the other sex, and rewrite as:

$$1 + \{\beta_F d + [d + (\gamma_M/\beta_M) d_*^2] \times \beta_M\}. \quad (1)$$

The resulting term $\gamma_M/\beta_M = \theta_M$, the ratio of quadratic and linear coefficients of the dose response in males, is the curvature of the dose response in males. Rather than estimating γ_M and β_M, we estimate θ_M and β_M in fitting Eq. (1) to the data. A similar derivation can be used to allow for curvature in the dose response among females, $\theta_F = \gamma_F/\beta_F$, by adding a quadratic term for females: $1 + \{[d + (\gamma_F/\beta_F) d_*^2] \times \beta_F + [d + (\gamma_M/\beta_M) d_*^2] \times \beta_M\}$.

The curvature parameter (θ_M or θ_F) will be large if the quadratic coefficient is significantly greater than zero and the linear coefficient is close to zero. When the linear coefficient is not significantly different from zero, an ordinary likelihood-based confidence interval for the curvature parameter is not appropriate because the confidence interval for the linear coefficient includes zero (*8*) and division by zero produces an infinite value of curvature. With such scenarios, if the estimate of the quadratic coefficient is significantly different from zero, the confidence region for the curvature parameter consists of two

components that exclude values around zero but extend to $\pm\infty$, i.e., $(-\infty, \theta^-]$ and $[\theta^+, +\infty)$, with the interval $\{\theta^- < \theta < \theta^+\}$ being the set of values that lie outside the confidence region for θ. We write this exclusion interval as ''] θ^-, θ^+ ['' to avoid confusion with the notation for ordinary confidence intervals. In these scenarios, we computed confidence intervals for θ^{-1} and θ to obtain the positive and negative components θ^- and θ^+ of the confidence region (the former by inverting the resulting bounds; see Supplementary Information; http://dx.doi.org/10.1667/RR15127.1.S1). In scenarios where the linear coefficient was significantly different from zero, we used the ordinary lower and upper confidence bounds (θ^L, θ^U) for θ. In scenarios where both the linear and quadratic coefficients are not significantly different from zero, the confidence region for the curvature is non-informative, $(-\infty, \infty)$, but we encountered few such scenarios.

Approaches to Assess Curvature

We used two methods of analysis to examine the influence of individual cancer sites on the all-solid-cancer curvature parameter. The first method was to exclude from all solid cancers individual sites one at a time, by treating them as censored. In addition to individual sites, we also excluded groups of sites that individually demonstrated the largest influence on the estimated curvature. Analyses based on this exclusion strategy were conducted with two approaches to background-rate adjustment. One approach was to parameterize the background rates in a similar way as was done for the solid cancer incidence analysis (*1*), where the log-linear parametric background model included sex-specific terms for the intercept, log of attained age (a linear-quadratic model in log age with, in addition, a quadratic spline with a knot at age 70) and a linear term in birth year. The background model also included interactions between city of residence and NIC status that were not sex-specific. The intercepts in this model are the sex-specific 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. We also examined the effect of adding a further interaction between city of residence and proximal-distal-exposure status (*4*), which we call ''distance'', with proximal (less than 3 km from the hypocenter) as the reference category. The other approach to background-rate adjustment was to stratify the background rates on the person-year categories corresponding to variables used in the parametric background model: city, sex, NIC status, attained-age group and age-at-exposure group as a surrogate for birth-year group (because all atomic bomb survivors were exposed in 1945, age at exposure is equivalent to birth year, an identity not applicable to cohort studies in general). Stratification induces interactions of all orders among the stratification variables. We also examined the effect of adding distance (proximal-distal-exposure status) with the stratified-background models, which would implicitly include the city-distance interaction.

The second method of analysis was to treat groups of sites as separate outcomes in the joint analysis described by Pierce and Preston (*9*). For this joint analysis, which was used only to study the dose-response curvature among males, we formed two groups of cancer sites. One group included sites that demonstrated large influence on the all-solid-cancer curvature in the male ERR that were also known to have features of background incidence that might deviate substantially from trends for all solid cancer in general (group ''M'' for misspecified). The other group consisted of all remaining sites of solid cancer (group ''O'' for other). A stratified person-year data set was created separately for each group with the addition of a group-identifier variable and an outcome variable (case counts within strata) for cancers within the group; then the two data sets were stacked and analyzed as a single data set. Analyses using the stacked data included separate intercepts for each group to account for the multiplicity in person-years. Joint analyses were based on the same parametric model as was used with individual site exclusions (without the city-distance interaction), except that we allowed all model parameters to differ between the two outcome groups.

We applied both methods of analysis to two sets of survivors: all LSS members or only male LSS members. The Epicure software (version 2.00.02; Risk Sciences International, Metcalfe, Canada) was used for analyses. Confidence regions are 95% likelihood-based regions and *P* values are from likelihood-ratio tests.

RESULTS

The estimated dose-response curvature parameter among males based on all LSS data was 1.16 ($P = 0.0024$) when the female dose response was constrained to be linear, as reported by Grant *et al.* (*1*). The estimated model intercept among males was 4.918, leading to an estimated annual incidence (at age 70 for birth year 1915) of $\exp\{4.918\} = 136.7$ per 10^5 persons per year.

Analyses based on Exclusion of Cancer Sites

Effects on all-solid-cancer ERR curvature among males of excluding selected individual sites of cancer are shown in Table 1 (a complete list of sites is provided in Supplementary Table S1; http://dx.doi.org/10.1667/RR15127.1.S1). The curvature was not eliminated by exclusion of any individual site, but there was large variation in the estimated curvature with exclusion of individual sites, including an increased magnitude of curvature with exclusion of some sites. Estimated dose responses are shown in Fig. 1 for all solid cancers (with no exclusion) and for the two extremes of individual-site exclusion from Table 1 (brain/CNS and prostate). When removal of a site led to a large reduction in the estimated curvature, there also tended to be a larger *P* value for the test of the curvature parameter and the lower confidence bound was closer to zero in the positive part of the confidence region. With exclusion of individual sites of female sex-specific cancers, there was little attenuation of the curvature estimate in males, but in some instances the curvature increased. In none of the scenarios shown in Table 1 was the estimated linear ERR parameter significantly different from zero; thus, two-component confidence regions for the curvature parameter are shown (these regions exclude zero but can be positive or negative, in either case being potentially infinite).

When we excluded sequentially larger groups of cancer sites comprising the two or more sites that were most influential on the all-solid-cancer curvature parameter among males, the magnitude of the estimated curvature parameter became progressively smaller (Table 2). With these exclusions of multiple sites of cancer, the linear ERR coefficient was significantly different from zero, so the usual confidence bounds on the curvature parameter could be computed. Excluding the three or more most influential sites resulted in negative lower 95% confidence bounds on the curvature estimate (equivalently, likelihood-ratio test *P* values greater than 0.05). Joint exclusion of brain/CNS, esophageal and thyroid cancers led to a 57% reduction in magnitude of the estimated curvature parameter; joint exclusion of brain/CNS, esophageal, thyroid and bone/

TABLE 1
Estimated Curvature of Radiation Dose Response among Males with Exclusion of Selected Individual Cancer Sites

Site excluded by censoring	ERR curvature parameter among males			No. of cases excluded	
	Curvature estimate	95% confidence region[a]	*P* value	Male	Female
None	1.16	] −8.40, 0.18 [	0.0024	0	0
Cancer sites with male cases					
Brain/CNS (including benign)	0.89	] −16.9, 0.11 [	0.0091	99	186
Esophagus	0.89	] −26.5, 0.12 [	0.0066	394	92
Thyroid	0.90	] −14.9, 0.12 [	0.0073	72	430
Bone/connective tissue	0.90	] −31.0, 0.12 [	0.0062	34	38
Non-melanoma skin cancer	0.96	] −8.90, 0.11 [	0.0090	195	321
Kidney	0.98	] −17.6, 0.15 [	0.0041	158	134
Gall bladder	1.03	] −13.1, 0.16 [	0.0035	84	270
Pancreas	1.04	] −12.0, 0.16 [	0.0035	306	417
Stomach	1.07	] −9.66, 0.14 [	0.0061	3,090	2,571
Colon	1.31	] −5.21, 0.18 [	0.0033	782	1,132
Liver	1.67	] −3.89, 0.24 [	0.0015	1,122	763
Prostate	1.99	] −3.64, 0.29 [	<0.001	851	0
Female-specific cancers					
Uterine corpus	1.12	] −9.01, 0.18 [	0.0028	0	244
Ovary	1.15	] −8.64, 0.18 [	0.0026	0	288
Cervix	1.27	] −6.93, 0.21 [	0.0018	0	886
Breast	1.29	] −6.72, 0.20 [	0.0019	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 (see Supplementary Information; http://dx.doi.org/10.1667/RR15127.1.S1).

connective tissue cancers led to 67% reduction; and exclusion of all five most influential sites led to an 80% reduction. The dose response with exclusion of brain/CNS, esophageal, thyroid and bone/connective tissue cancers, shown in Fig. 1 (as ‘‘group of four’’), is close to the linear dose response for all solid cancers combined.

In an analysis of all solid cancer restricted to only male LSS members, the background-rate intercept for males changed from 4.918 [standard error (SE) 0.0274] with the full LSS cohort to 4.885 (SE 0.0375), and the male-specific background parameters (the three parameters of the linear-quadratic-spline in log age and the birth-year effect) did not change appreciably. However, the two background parameters that are not sex-specific (the interactions between city and NIC) changed notably when females were excluded: from −0.0379 (SE 0.0180) to −0.0301 (SE 0.0263) in Hiroshima (21% change) and from −0.101 (SE 0.032) to −0.116 (SE 0.044) in Nagasaki (15% change). In addition, the male ERR curvature parameter was closer to zero with the male LSS subset than with the full LSS cohort (Table 3), and the linear term in the linear-quadratic dose response increased from 0.094 with the full LSS to 0.115 in the male-only subset. (Results of individual-site exclusion in the male-only subset are shown in Supplementary Table S2; http://dx.doi.org/10.1667/RR15127.1.S1) When the five most influential sites were jointly excluded from the male-only subset, the estimated curvature all but vanished (Table 3) and the linear term in the dose response was 0.24. When the interaction between city and distance group was added to the background model, evidence for curvature diminished even further. Joint exclusion of the five most influential sites in a fit restricted to males resulted in a negative (though not statistically significant) estimate of the curvature parameter (Table 3) and linear ERR term 0.31 (SE 0.10), which is close to the purely linear ERR for males (0.33) in the analysis by Grant *et al.* (*1*). Similar reductions in curvature were observed with the stratified-background-rate models (Table 3).

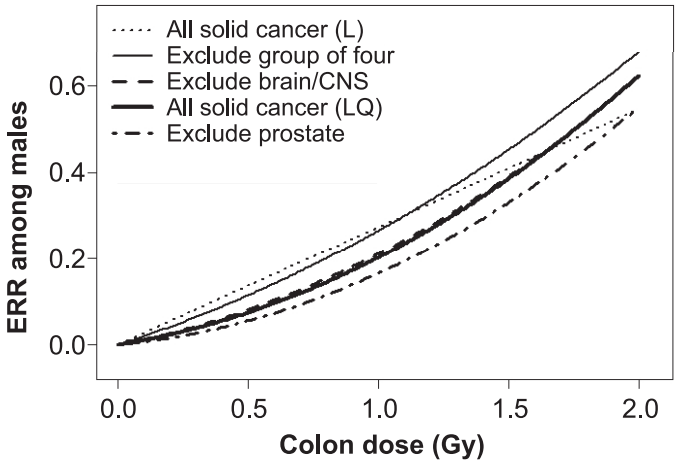

FIG. 1. Fitted dose-response curves obtained with exclusions from all solid cancer of various sites. The linear and linear-quadratic models fit to all solid cancer are included for comparison. The ‘‘group of four’’ represents simultaneous exclusion of brain/CNS, esophagus, thyroid, and bone/connective tissue cancers.

Effects of excluding individual sites of cancer on inference about curvature in the dose response among females are shown in the Supplementary Table S3 (http://

TABLE 2
Estimated Curvature of Radiation Dose Response among Males with Exclusion of Increasingly Larger Groups of Influential Cancer Sites (Using Data from all LSS Participants)

Sites excluded by censoring	ERR curvature parameter among males			No. of cases excluded	
	Curvature estimate	95% confidence region[a]	*P* value	Male	Female
None	1.16	] −8.40, 0.18 [	0.0024	0	0
Brain/CNS and esophagus	0.67	(0.047, 23.3)	0.023	493	278
Brain/CNS, esophagus, and thyroid	0.50	(−0.0066, 7.10)	0.056	565	708
Brain/CNS, esophagus, thyroid, and bone/connective tissue	0.38	(−0.044, 3.69)	0.10	599	746
Brain/CNS, esophagus, bone/connective tissue, thyroid, and non-melanoma skin	0.23	(−0.11, 2.35)	0.28	794	1,067

[a] The confidence region for the curvature parameter is the ordinary confidence interval in all scenarios except for the fit with no cases excluded because the estimate of the linear coefficient was significantly different from zero (see footnote *a* to TABLE 1).

dx.doi.org/10.1667/RR15127.1.S1). None of the sites individually, when excluded, led to significant curvature among females. Removal of the two most influential sites (breast and stomach), however, resulted in a significant curvature parameter among females [0.54; 95% confidence interval (CI) 0.066–2.49], and further exclusion of thyroid cancers led to an estimate of curvature among females that was comparable to the magnitude of estimated curvature for all solid cancers among males (1.29; 95% confidence region $\{(-\infty, -9.30], [0.20, +\infty)\}$; Supplementary Table S4). With the exclusion of breast, stomach and thyroid cancers combined, the linear ERR term among females was 0.19 (SE 0.12), substantially less than the estimated linear ERR term for females with all solid cancers combined and no quadratic parameter in the dose-response model (0.64; SE 0.063).

Joint Analysis

Among the five sites of cancer that were most influential on inference about curvature among males, three sites (thyroid, brain/CNS and bone/connective tissue cancers), although having generally low overall incidence, constitute a greater proportion of total incidence at young ages than at older ages (*10–12*). Background rates at these sites therefore have the potential to be misspecified when a single background-rate model is fit to all solid cancer combined.

TABLE 3
Estimated Curvature of Radiation Dose Response among Males under Various Modeling Conditions

Cohort	Outcome (cancer group)	Background model	Male curvature parameter	95% confidence region[a]	*P* value
		Parametric background model			
All LSS	All solid cancer	Original model	1.16	] −8.40, 0.18 [	0.0024
	Exclude five most influential		0.23	(−0.11, 2.35)	0.28
Males only	All solid cancer		0.84	] −14.6, 0.06 [	0.023
	Exclude five most influential		0.075	(−0.21, 1.49)	>0.5
All LSS	All solid cancer	With city-distance interactions added	0.82	(0.11, 129.)	0.0069
	Exclude five most influential		0.17	(−0.13, 1.60)	0.39
Males only	All solid cancer		0.49	(−0.030, 7.18)	0.079
	Exclude five most influential		−0.021	(−0.23, 0.76)	>0.5
		Stratified background model			
All LSS	All solid cancer	Stratified on original variables[b]	1.00	] −9.90, 0.14 [	0.005
	Exclude five most influential		0.19	(−0.13, 2.09)	0.36
Males only	All solid cancer		0.71	] −35.5, 0.018 [	0.039
	Exclude five most influential		0.038	(−0.22, 1.25)	>0.5
All LSS	All solid cancer	Further stratified on distance [c]	0.55	(0.032, 6.25)	0.028
	Exclude five most influential		0.063	(−0.17, 0.94)	>0.5
Males only	All solid cancer		0.34	(−0.074, 3.30)	0.16
	Exclude five most influential		−0.058	(−0.24, 0.57)	>0.5

[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 (see Supplementary Information; http://dx.doi.org/10.1667/RR15127.1.S1). The notation ‘‘(,)’’ indicates the usual confidence interval.

[b] Variables used in the original parametric background-rate model included city, sex, not in city (NIC), attained age and birth year.

[c] Stratification implicitly imposes interactions among all stratum variables, so the city-distance interaction is subsumed in stratification when distance is included as a stratifying variable.

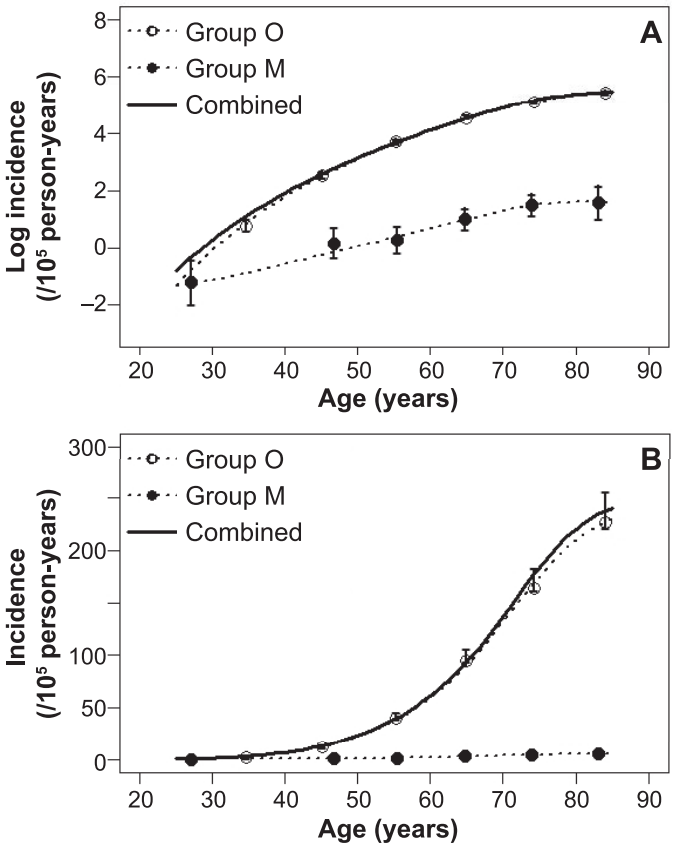

FIG. 2. Fitted values of age-specific log incidence (panel A) and incidence (panel B) among males in the two groups of cancers defined for the joint analysis: M (thyroid, brain/CNS, and bone/connective tissue cancers; solid points) and O (all other cancers; open circles). Lines were drawn with the fitted parameters (intercept, linear age, quadratic age and age spline) from the fit of the full parametric model incorporating continuous age, birth year, etc., as described in the text. Points were obtained from fits of the same model with continuous age replaced by six age groups defined by cut-points at 40, 50, 60, 70 and 80 years. Ages on the abscissa for these points are person-year-weighted mean ages calculated from cells with at least one cancer case in the person-year table. Error bars are 95% likelihood-based confidence intervals for the estimated log rates in each age group. The solid line (''combined'') is the result of the analysis with a single background-rate model for all solid cancers combined.

We therefore conducted a joint analysis in which we grouped these three sites (group ''M''; 859 cases) separately from all other solid cancers (group ''O''; 21,679 cases). Note that this grouping is used merely for assessment of the effect of background-rate estimation on dose-response curvature; as reported by Pierce and Preston (*9*), one should use appropriate choices of cancer classes to obtain biologically meaningful results in a joint analysis. For the joint analysis we used all LSS members and the same parametric model as was used by Grant *et al.* (*1*), except that we added interactions of cancer group (M or O) with all parameters in the model. The resulting models are completely heterogeneous in terms of cancer group (i.e., there are no parameters with values that are constrained to be equal in both groups). As expected, background-rate parameters, especially those related to age, differed substantially between the two groups (see Supplementary Table S5; http://dx.doi.org/10.1667/RR15127.1.S1).

The higher proportion of total incidence that is due to cancers in group M at young ages, relative to that at older ages, is striking, reflected by near-equal log incidence in the two groups at young ages (Fig. 2A). The difference in incidence between the two groups at early ages is not easily seen with untransformed incidence (Fig. 2B), but importantly, the estimated annual incidence of all solid cancers among males at age 70 with birth year 1915 in the joint analysis, $\exp(4.877) + \exp(1.306) = 131.2 + 3.69 = 134.9$ per 10^5 persons (the sum of the estimates from the two mutually exclusive groups), is lower than that obtained with a single background-rate model for all solid cancers combined (136.7 per 10^5). For group O in the joint analysis, the linear ERR coefficient was significantly different from zero, and the estimated curvature parameter was 0.53 (less than one half of the value, 1.16, obtained with all solid cancers combined) with confidence region (0.004, 9.06) (the estimate of the linear coefficient was significantly different from zero) and likelihood ratio test $P = 0.047$. In other words, after separating out the influential sites in group M, the evidence for dose-response curvature among males in the remaining solid cancers as a group was not very strong. A male ERR curvature parameter could not be estimated for group M, presumably due to a small number of radiation-related excess cases (estimated number of excess cases was 64 in group M). Given that the curvature parameter for group M could not be fit, as a check we also excluded from all solid cancers the three sites of group M (in the same way as with the Table 2 analyses): the resulting curvature among males was 0.53 with 95% confidence region (0.004, 9.06) and likelihood ratio $P = 0.047$ (identical to the values for group O in the joint analysis).

Illustration of Influence of the Background Model on Curvature

The ''intercept'' of the ERR dose-response curve is determined by the fitted background model (the estimated incidence at dose zero). Although the difference in overall intercept of the background-rate model for males (136.7 per 10^5 vs. 134.9 per 10^5) seems small, to further examine how the estimated background model affects the shape of the dose response, we estimated the ERR dose-response among males with all other model parameters fixed at their estimated values and with the value of the male background-rate intercept fixed at various values around these two levels. The difference in the two intercept levels explained approximately 25% of the ERR curvature parameter estimate among males (Table 4). To better visualize the effect of the fitted background model on the shape of the ERR dose response, we transferred estimation of the ERR dose-response intercept from the background model to the ERR model by fixing the overall background

TABLE 4
Effect of Background-Rate Intercept on Magnitude of Estimated ERR Curvature among Males

Intercept (log incidence at age 70 for survivor born in 1915)	Estimated ERR curvature parameter
4.918	1.163
4.915	1.103
4.910	0.996
4.905	0.904
4.900	0.823

intercept and estimating the ERR for all dose groups including the zero-dose group (i.e., not setting the zero-dose group as the reference group). Assuming that the combined background rate (at age 70 for a survivor born in 1915) estimated with the two-group model is more accurate than that estimated with the single all-solid-cancer model, we fit the all-solid-cancer model with the male background-rate intercept fixed at $\log(134.9) = 4.905$. The estimated ERR in the zero-dose group, which is an estimate of possible error in the ERR intercept due to over-estimation of the background-rate intercept, was 1.1×10^{-2} (Fig. 3). In the two-group model with the same overall background incidence, i.e., the two background intercept parameters for males fixed at 4.88 (Group O) and 1.31 (Group M), the estimated ERR in the zero-dose group was essentially zero (-1.2×10^{-3}; Fig. 3). Although the estimated ERRs for dose groups up to 1 Gy in Fig. 3 are higher with the all-solid-cancer model than with the two-group model, in the group with doses above 1 Gy (not shown), the estimated ERR with the all-solid cancer model (0.424) was lower than with the two-group model (0.484). Thus, overestimation of the ERR with the single all-solid-cancer model only occurred at low doses, so the greater curvature with the single all-solid-cancer model appears to be due to the bias in the ERR intercept (which we have demonstrated to be related to background-rate-model heterogeneity) rather than to heterogeneity in estimated ERR at high doses.

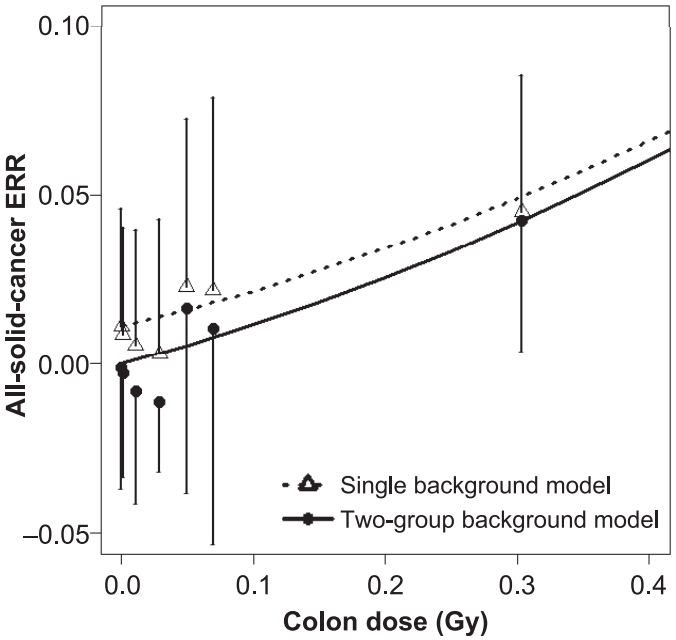

FIG. 3. ERR dose response among males for all solid cancer combined, fit with the parametric background model but with the overall background-rate intercept for males fixed at its value estimated in the two-group joint analysis. Points are estimated ERR in dose strata defined by {[0], (0, 0.005), [0.005, 0.02), [0.02, 0.04), [0.04, 0.06), [0.06, 0.08), [0.08, 1.0) and 1.0+ Gy}, where ''['' connotes ''inclusive of'' and '')'' connotes ''exclusive of'': triangles are with a single background model common to all solid cancers, and closed circles are with the two-group joint analysis background model. ERR for the 1.0+ Gy group is not shown, to allow for focusing on the low-dose region. Confidence intervals are 95% Wald bounds; to avoid clutter, only one side of each interval is shown. Lines are the fitted ERR dose responses based on the two-parameter ERR model (linear and curvature parameters) with intercept equal to the estimated ERR in the zero-dose stratum from the fit of each of the two background-rate models.

DISCUSSION

Until recently, it has generally been thought that solid cancer incidence in the atomic bomb survivors provides scant evidence of nonlinearity in the radiation dose response, even at low doses, although it has been suggested that certain sites of solid cancers might exhibit curvature (*13*). Curvature in the dose response has become apparent in analyses of LSS solid cancer mortality (*5*), and although it was not reported there whether the magnitude of curvature differed by sex, a later analysis of those data (*2*) provided sex-specific estimates of linear and quadratic terms that led to similar estimates of curvature in males and females. Therefore, the finding by Grant *et al*. (*1*) that males, but not females, exhibit curvature in the all-solid-cancer incidence dose response for radiation is intriguing but difficult to interpret. We did not examine curvature in the dose responses of individual cancer sites, but by excluding individual sites of cancer from all solid cancers as a group we observed large variation in the magnitude of the estimated all-solid-cancer dose-response curvature parameter among males and among females. This supports the conclusion of Grant *et al*. (*1*) that curvature might not be a common property of all solid cancer in general but rather that there might be heterogeneity across cancer sites in the shape of the dose response.

It is also possible that effect modification of the radiation dose response differs among sites of cancer. Our results further suggest that the curvature, or lack thereof, could be to some extent influenced by the use of a single background-rate model for all solid cancer. The estimated male curvature for all solid cancer incidence was greatly reduced when we used a joint analysis incorporating a separate background-rate model for a group of three cancer sites (thyroid, brain/CNS and bone/connective tissue cancers) that have age-specific incidence rates substantially

different from those of all solid cancers as a single group. Thyroid carcinoma tends to occur relatively more frequently at younger ages than most carcinomas (*10*). Thyroid cancer is also more common among women than among men (*14*). Brain and CNS tumors are particularly common among adolescents and young- to middle-aged adults (*11*). Bone cancer tends to occur earlier in life than solid cancers in general (*12*). Curvature in the female dose response for all solid cancer incidence emerged when breast, stomach and thyroid cancers were excluded. Whether this is due to background-rate heterogeneity or a heavy influence of linearity in the dose response at these sites remains to be determined, but it has been noted previously that breast and thyroid cancers have a strong effect on the estimation of curvature in the solid cancer dose response (*15*).

The problem with estimating a single model for all solid cancers, and its influence on curvature of the dose response, is both simple and complex. A biased estimate of the background rate will lead to a biased estimate of the dose response at zero dose (the dose-response intercept) and, therefore, a biased estimate of the dose response overall, and if the bias in the dose-response intercept is large it could induce or increase an estimate of curvature (*3*, *4*). Although altering the background-rate intercept alone, as we illustrated here, does not capture the subtleties and complexities of how the other estimated background-rate parameters influence the overall intercept, our analyses with different background-rate intercepts demonstrate how sensitive the curvature-parameter inference is to the value of the estimated background rate. Because of the complex nature of the background-rate models, it is difficult to pinpoint exactly where the source of bias comes from. It could come from several sources, the age model, the birth-year model or the categorical adjustments for city and distance, if any of these are misspecified. Furthermore, we ignore the fact that doses to different organs differ by relatively constant proportions, and shielding of neutrons varies by depth of organ. Matters related to the role of neutrons are being investigated at RERF but are too complex to address in this work.

Similar considerations related to heterogeneity might apply in the case where curvature truly exists but cannot be detected because of background heterogeneity. This might explain the apparent lack of curvature in the all-solid-cancer dose response among females and the reason that curvature in the female dose response emerged with exclusion of certain cancer sites. An underestimate of the dose-response intercept could reduce the magnitude of the estimated curvature parameter, as could the failure to account for high-dose leveling off of the dose response (*16*). These issues should be of concern whether one is examining an ERR model, which was examined empirically here, or an EAR model, since the EAR model shares the same background rate model and is merely an alternative mathematical expression of the total rate (*17*).

Even without excluding individual sites of cancer, more-flexible background-rate adjustments (including interaction between distance categories and city in the parametric model or using stratification, which implicitly includes interactions) resulted in lower curvature estimates among males for all solid cancers collectively. As noted by French *et al.* (*4*), distance might be correlated with unmeasured confounders, so failure to adjust for distance could result in a biased intercept estimate. These findings make it clear that careful attention needs to be paid not only to age-time parameters of the background-rate model, but also to categorical factors affecting the background rate.

Analysis of nonlinearity in the dose response is a natural goal of site-specific analyses of radiation risk for cancer, and such analyses should benefit from using joint analysis methods (illustrated here) to take full advantage of the information available from all other solid cancers by treating other sites of cancer as competing risks rather than as causes of censoring (due to the restriction to first primary cancers). The most influential sites revealed in the current analysis of LSS data would be candidates for such curvature assessment, although nonlinearities might also exist with some less influential sites. A nonlinear dose response has been reported for non-melanoma skin cancer (*18*). Relatively little is known about risk of esophageal cancer in the atomic bomb survivor cohort, although Preston *et al.* (*19*) noted that background rates of esophageal cancer differed markedly between men and women, consistent with an etiological effect of smoking. Small numbers of cases at some cancer sites could result in low statistical power to detect significant curvature in the dose response even if curvature exists. On the other hand, inability to precisely model the background rate with small numbers of cases could result in inadequate background-rate adjustment, leading to spurious inference regarding curvature. In addition, inadequate modeling of the background rates can result in biased estimation of effect modification parameters (*20*), and effect modification might be poorly estimated with small numbers of radiation-related excess cases; these limitations could also influence inference about the dose response. Furthermore, individual site-specific analyses do not facilitate direct comparison of the shape of the dose-response function among sites of cancer.

Although there may be some heterogeneity among cancer sites in terms of ERR in a linear model (*21*), extreme heterogeneity such as we observed with the estimated curvature parameter is not typical of linear radiation ERR estimates derived from the atomic bomb survivor data. In the current analysis, individual sites or groups of sites had little influence on the estimated slope of a linear ERR model (i.e., assuming that the quadratic coefficient, and thus the curvature parameter, is zero). For example, the linear ERR per Gy for males with exclusion of each of the five most influential sites individually (brain/CNS, esophagus, bone/connective tissue, thyroid and non-melanoma skin cancer) with data for both sexes included was: 0.27 (CI 0.19–0.37),

0.28 (CI 0.19–0.38), 0.27 (CI 0.19–0.37), 0.30 (CI 0.21–0.40) and 0.24 (CI 0.16–0.34), respectively. The linear ERR for males with exclusion of all five of these sites simultaneously was 0.28 (CI 0.19–0.38). These are all close to the estimated linear ERR per Gy for males reported by Grant *et al*. (*1*) for all solid cancer, 0.27 (CI 0.19–0.37). Grant *et al*. (*1*) also reported a linear ERR for females of 0.64 (CI 0.52–0.77). That the linear ERR for females is substantially larger than that for males might be a reason that the influence of heterogeneity in background rates among individual sites did not lead to significant curvature in the dose response among females, as it did among males. Even if such background-rate heterogeneity led to large variation in the female quadratic ERR parameter, the estimated curvature among females would be much smaller than in males because of the larger linear coefficient.

Our analysis has the following strengths and potential limitations. A key strength is our use of the full cohort data when focusing on a subset of cancer sites, by using a joint analysis that allows estimating and testing differences in parameters across groups of sites. Because the joint analysis is based on first cancers, it is equivalent to a competing-risks analysis (*22*). A second strength is the use of stratification for background-rate estimation, which reduces the potential for background-rate misspecification. A third strength is the inclusion of distance category, which might be associated with unmeasured confounders (*4*). One limitation of our analyses is that stratification of background rates can result in loss of efficiency due to imbalance in apportionment of numbers of events across strata (*23*). Given the large amount of LSS data, however, few strata had apportionment ratios of zero (no cases) or infinity (cases only). A second limitation is that our selection of cancer-site groups for the joint analysis was ad hoc, and indeed individual sites within a group might not share common background-rate or dose-response parameters. A third limitation is that we did not attempt to do careful background-rate or dose-response modeling of individual cancer sites that account for heterogeneity in background rates. However, our primary objective was to study possible sources of, or causes of, curvature or lack of curvature in the estimated dose response for all solid cancers combined. Careful modeling is the goal of individual site-specific analyses that are ongoing (*24–27*). A fourth limitation is that, although several methods exist for accounting for random dosimetry error, including a Bayesian approach (*16*) and a simulation-extrapolation approach (*28*), we used only the method of Pierce *et al*. (*6*) because our goal was to further understand the results of Grant *et al*. (*1*), who employed that method. Finally, our analysis focused exclusively on the LSS cohort. Although our conclusions regarding combining all solid cancers as a single outcome might apply to other studies of radiation-exposed populations, effects of background heterogeneity might differ by population. Furthermore, studies that lack a sufficiently large number of cases for detailed site-specific analyses might need to rely on all solid cancer as the primary outcome. The results of our investigation suggest that the results of such analyses should be interpreted carefully and potential biases arising from background-rate heterogeneity should be examined.

Joint analysis with Poisson regression and person-year data is useful for overcoming one potential limitation of site-specific analyses: inefficiency due to informative censoring, in which the censoring times might contain information about risk. Joint analysis allows one to fit separate background-rate models to multiple sites of cancer while at the same time assuming a common form of radiation dose response (if such an assumption is appropriate), thereby increasing power. Identifying groups of cancers with common background rates would allow combining sites to reduce the number of parameters and increase power for assessing risk and describing risk modification. However, the Poisson regression approach to joint analysis does not address dependent-censoring bias, in which the censoring time is not independent of the event-onset time, because the piecewise-constant hazard approximation used in the derivation of the Poisson model for grouped event-time data is based on the assumption that failure times and censoring times are independent (*29*). Dependent censoring can exist because deaths from non-cancer diseases, which are treated as censored in analyses of cancer incidence if they occur prior to a cancer diagnosis, are also related to radiation exposure. Further work, following perhaps on that of Staplin *et al*. (*30*), is needed to identify and address potential bias due to dependent censoring in analyses of risk based on Poisson regression of person-year data.

The published literature contains several applications of the joint analysis method. Little (*31*) found significant heterogeneity by cancer type in the relative risk for radiation and in effect modification of the risk by sex and age at exposure. Richardson and Hamra (*32*) used the approach to study radiation effects on two subtypes of kidney cancer (cancer of the renal parenchyma and cancer of the renal pelvis and ureter). Little *et al*. (*33*) used the method with data on a predominantly male cohort with fractionated, partial-body irradiation for peptic ulcer treatment and found evidence of downward curvature in the dose response for all cancers, pancreatic cancer, and all cancers excluding stomach, pancreas, lung and leukemia (the sites used in their joint analysis). An alternative, hierarchical approach to joint analysis with Poisson regression was proposed by Richardson *et al*. (*34*), whereby parameters are estimated in a Bayesian framework that results in greater precision of parameter estimates for outcomes with small numbers of observations. An advantage of the hierarchical-regression approach is that one does not need to assume homogeneity of effects across sites by grouping sites together or by assuming that certain sites share a common parameter. On the other hand, the joint analysis of Pierce and Preston (*9*)

may be implemented easily with standard Poisson regression software.

In conclusion, although analyses of the Life Span Study data have consistently shown that radiation exposure is significantly associated with elevated risk of mortality and solid cancer incidence (*35*), our results suggest that treating all incident solid cancer as a single outcome might not be the most effective approach for determining the shape of the radiation dose response, especially at low-dose levels. Rather than leading one to question results of the LSS, this finding should be viewed as a positive new juncture in the evolution of atomic bomb survivor studies. Just as the earliest studies relied on contingency table methods, regression methods then became available that allowed explicit estimation of the dose response, and with nearly 60 years of follow-up there is now extensive information for estimating background-rate parameters and radiation-risk modification parameters, so that heterogeneity across cancer sites in these components of the cancer incidence models can now be accommodated. Joint analysis can increase power for inference about radiation risk at individual cancer sites by borrowing strength across sites, if grouping of sites is prudently guided by consideration of the cancer epidemiology and radiation sensitivities of individual organs. Such an approach should aid in determining the true shape of the radiation dose response for individual sites of cancer, as well as risks at low doses, which are the focus of ongoing research.

SUPPLEMENTARY INFORMATION

The Supplementary Information file contains six sections. Section 1 describes the calculation of a confidence region for the curvature parameter estimate, which is complicated by the fact that values of estimated curvature that are consistent with the data (i.e., in the confidence region for the estimated curvature parameter) can be infinite if the estimate of the linear coefficient is not significantly different from zero, because the linear coefficient is the denominator of the ratio that defines the curvature parameter. Section 2 provides complete results showing effects on curvature among males with single-site exclusion for all sites of solid cancer in the Life Span Study (LSS), not just the most influential sites shown in Table 1. Section 3 provides similar results showing effects on curvature among females. Section 4 presents a simple hypothetical example to illustrate how the intercept affects inference about curvature in the dose response. Section 5 provides estimated parameters of the background-rate models for the two groups (M and O) in the joint analysis. Section 6 explains the adjustment for random dose-estimation error that is needed when using a quadratic term in dose. The explanation is provided because this subtle but important fact might not be generally recognized.

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