TABLE 2
Distribution of Person-Time, Average Distance from Hypocenter, Observed and Observed/Expected Deaths due to Leukemia by Estimated Dose

Dose (Gy)	<0.005	0.005–<0.1	0.1–<0.5	0.5–<1	1–<2	2+	Trend[a]
Leukemia: all types							
Rate ratio (90% CI)	1.0 (referent)	1.0 (0.7, 1.5)	1.4 (0.9, 2.1)	3.3 (2.1, 5.1)	6.7 (4.4, 10.4)	17.3 (11.2, 26.7)	4.7 (3.5, 6.4)
Observed	99	73	43	29	33	33	310
AML							
Rate ratio (90% CI)	1.0 (referent)	0.8 (0.5, 1.3)	0.8 (0.4, 1.4)	1.5 (0.7, 3.1)	5.7 (3.2, 10.4)	14.5 (8.0, 26.4)	4.3 (2.7, 6.6)
Observed	39	31	14	8	16	16	124
CML							
Rate ratio (90% CI)	1.0 (referent)	4.5 (1.1, 45.2)	8.5 (2.1, 86.6)	17.8 (4.1, 185.6)	23.8 (5.1, 253.4)	59.1 (12.7, 630.2)	6.4 (3.0, 13.7)
Observed	13	15	13	7	5	5	58
ALL							
Rate ratio (90% CI)	1.0 (referent)	1.5 (0.3, 15.5)	1.4 (0.2, 15.8)	7.6 (1.3, 81.9)	10.2 (1.4, 116.3)	10.4 (0.8, 138.6)	3.7 (0.8, 13.0)
Observed	6	5	2	3	2	1	19
ATL							
Rate ratio (90% CI)	1.0 (referent)	1.9 (0.6, 6.8)	0.9 (0.1, 5.4)	0.9[b] (0.1, 5.0)	— (—,—)	— (—,—)	−0.2 (nd, 1.78)
Observed	7	6	1	1	0	0	15
Person-years/10^4	137.6	109.9	22.9	13.6	7.5	3.1	
Distance[c]	4007	2152	1644	1287	1156	958	

[a] Estimated ERR/Gy based on a linear ERR model without effect modification of the form $ERR(d) = \beta d$.
[b] The values reported are for the dose category 0.5+ Gy; the upper three dose categories were coalesced because the observed number of ATL deaths was zero in the categories 1–2 Gy and 2+ Gy.
[c] Person-time weighted mean distance from hypocenter, in meters.

effect of time since exposure to vary with age at exposure, leading to a regression model of the form

$$ERR(d,e,t) = (\beta d + \theta d^2)\exp[\gamma e' + \delta_1 t + \delta_2 t^2 + \delta_3 t^3 + \delta_4 (t-15)^3_+ + \delta_5 (t-30)^3_+ + \delta_6 (t-45)^3_+ + \phi_1 e' t + \phi_2 e' t^2 + \phi_3 e' t^3 \; \phi_4 e' (t-15)^3_+ + \phi_5 e' (t-30)^3_+ + \phi_6 e' (t-45)^3_+],$$

where, for any k, $(t-k)^3_+ = (t-k)^3$ if $(t-k) > 0$, 0 otherwise. The terms for the main effect of time since exposure, $\delta_1 - \delta_6$ contributed little to goodness of the model fit and were excluded from subsequent analyses (LRT = 2.5, 6 *df*; $P > 0.50$); with this parameterization the ERR remains constant with time since exposure for those exposed at ages 30+ years. Splines with fewer knots tend to imply smoother functions; the knots at 15 and 45 years since exposure could be omitted without substantial reduction in the goodness of model fit (change in residual deviance = 1.6, 2 *df*), leading to a model of the form $ERR(d,e,t) = (\beta d + \theta d^2)\exp[\gamma e' + \phi_1 e' t + \phi_2 e' t^2 + \phi_3 e' t^3 + \phi_5 e' (t-30)^3_+]$ (AIC = 1995.0). Several previous analyses of leukemia mortality among LSS survivors (*8, 9, 19*) have modeled variation in the excess risk of leukemia with time since exposure as a monotonic function of t or $\log(t)$. However, neither a model of the form $ERR(d,e,t) = (\beta d + \theta d^2)\exp[\gamma e' + \delta t + \phi e' t]$ nor a model of the form $ERR(d,e,t) = (\beta d + \theta d^2)\exp[\gamma e' + \delta log(t) + \phi e' log(t)]$ produces as small an AIC statistic (AIC = 2000.3 and AIC = 1998.0, respectively), and a nested model with a monotonic function of t, of the form $ERR(d,e,t) = (\beta d + \theta d^2)\exp[\gamma e' + \phi e' t]$, does not fit as well (LRT = 10.7, 3 *df*, $P = 0.01$).

There was no evidence of heterogeneity in the dose–response association by sex (LRT = 0.0, 1 *df*, $P = 0.92$). There was, however, evidence of heterogeneity in the dose–response association by city (LRT = 6.8, 1 *df*, $P = 0.01$).

Table 3 reports the parameter estimates for the final model for leukemia of all types. The estimated model coefficients $\hat{\beta}$ and $\hat{\theta}$ describe the linear-quadratic dose–response function; $\hat{\gamma}$ describes the main effect of age at exposure. The terms $\hat{\phi}_1$, $\hat{\phi}_2$, $\hat{\phi}_3$, and $\hat{\phi}_5$ describe the effect of time since exposure among those <30 years of age ATB (at older ages ATB, these terms equal zero since $e' = 0$). The term $\hat{\omega}_c$ is the city effect; the estimated ERR at 1 Gy for cohort members from Hiroshima was approximately threefold larger than the estimate for those from Nagasaki.

Figure 1 illustrates the predicted ERR/Gy for leukemia of all types as a function of time since exposure for people exposed at ages 10, 20 and 30+ years. Under the fitted model, the ERR/Gy diminishes in magnitude with increasing age at exposure through age 30 years. For those exposed at ages <30 years, the estimated ERR/Gy rises to a peak 7 years after exposure.

Table 4 reports the estimated numbers of background and excess deaths due to leukemia of all types. Of the 310 leukemia deaths observed, the fitted model suggests that approximately 103 were excess deaths while 207

TABLE 3
Preferred Models for Leukemia by Category of Cause of Death[a]

Cause	Leukemia: all types							
Model	$ERR(d,c,e,t) = \beta d + \theta d^2)(1 + \omega c)\exp\left[\gamma e' + \phi_1 e' t + \phi_2 e' t^2 + \phi_3 e' t^3 + \phi_5 e'(t-30)_+^3\right]$							
Parameter	β	θ	ω	γ	ϕ_1	ϕ_2	ϕ_3	ϕ_5
Estimate	1.55	0.83	−0.54	−1.06	−0.20	0.02	−3E-4	7E-4
(90% CI)	(0.63, 2.94)	(0.29, 1.53)	(−0.79, −0.21)	(−2.81, 0.74)	(−0.50, 0.07)	(0.00,0.03)	(−6E-4, −9E-5)	(2E-4, 1E3)
Cause	Acute myeloid leukemia							
Model	$ERR(d,e,t) = (\theta d^2)\exp\left[\gamma e' + \left(\phi_1 e' t + \phi_2 e' t^2\ {}_3 e' t^3 + \phi_5 e' t(t-30)_+^3 + \phi_6 e'\right)(t-45)_+^3\right]$							
Parameter	θ	γ	ϕ_1	ϕ_2	ϕ_3	ϕ_5	ϕ_6	
Estimate	2.81	7.80	−1.91	0.11	−2E-3	4E-3	−0.01	
(90% CI)	(1.63, 4.64)	(1.45, nd)	(nd, −1.65)	(nd, 0.12)	(nd, −2E-3)	(2E-3, 9E-3)	(−0.02, −3E-3)	
Cause	Chronic myeloid leukemia							
Model	$ERR(d) = (\beta d)$							
Parameter	β							
Estimate	6.39							
(90% CI)	(3.00, 13.71)							
Cause	Acute lymphatic leukemia							
Model	$ERR(d) = \beta d$							
Parameter	β							
Estimate	3.70							
(90% CI)	(0.81, 12.99)							
Cause	Adult T-cell leukemia							
Model	$ERR(\ ) =$							
Parameter								

[a] Where d is estimated marrow dose in Gy, c is city and coded −1 for Hiroshima and 1 for Nagasaki, e is age at time of bombing in years, $e' = \min[0, (e - 30)/10]$, and t is time since exposure in years.

were classified as background cases. The $AF_{0.005\ Gy}$ of leukemia was close to unity at young attained ages, suggesting that nearly all of the leukemia deaths observed among those exposed at young ages (e.g. <5 years) in the first years of follow-up were excess cases associated with radiation exposure. The $AF_{0.005\ Gy}$ was 0.67 in the period 1950–1960 and 0.34 in the most recent decade of follow-up (1991–2000). For those survivors with estimated doses of 0.5 Gy or higher, the $AF_{0.005\ Gy}$ was greater than 0.50. The model-based time-averaged $AF_{0.005\ Gy}$ was 0.49, and the corresponding time-averaged EAR estimate was 2.4 cases per 10^4 PY Gy.

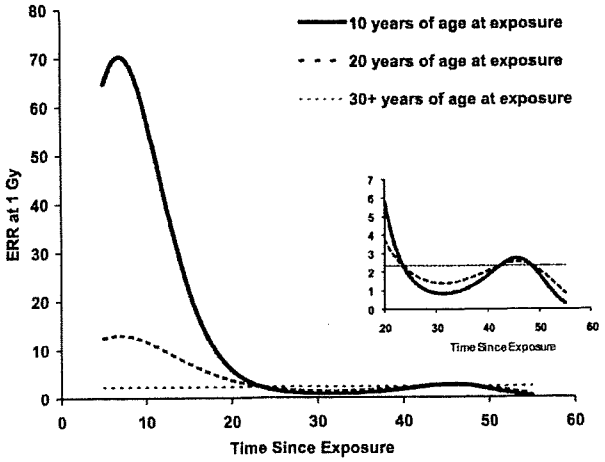

FIG. 1. Predicted city-averaged ERR at 1 Gy for leukemia (all types) as a function of age at exposure and time since exposure. Inset provides an expanded view of ERR estimates for the period 20 or more years after exposure.

Acute Myeloid Leukemia

There were 124 deaths due to AML included in these analyses; no deaths due to AML were observed at attained ages less than 10 years (Table 1). Table 2 reports estimated rate ratios for mortality due to AML by categories of bone marrow dose, with people who had doses <0.005 Gy serving as the reference category. Estimated rate ratios were less than unity among people with estimated doses of 0.005–<0.1 Gy and 0.1–<0.2 Gy while rate ratios greater than unity were observed among people in the highest three estimated dose categories. Table 2 also reports the estimated dose–response association derived via a linear ERR model without effect modification; there is a significant association between estimated dose and mortality due to AML (LRT = 76.5, 1 *df*, $P < 0.001$). Model fit improved upon inclusion of a quadratic term to the dose–response function (LRT = 15.0, 1 *df*, $P < 0.001$). In fact, a comparison of a model in which the dose–response function was purely quadratic to a model with a linear-quadratic dose–response function indicated that inclusion of a linear term contributed little to the model fit (LRT = 0.3, 1 *df*, $P < 0.50$). The analyses of effect modification, described below, were based upon a model with a purely quadratic radiation dose–response function.

TABLE 4
Predicted Number of Background[a] Deaths, Excess Deaths, and the Attributable Fraction of Deaths due to Leukemia of all Types among those Exposed to >0.005 Gy ($AF_{0.005}$)[b]

	Leukemia: all types		
	Fitted background	Fitted excess	$AF_{0.005}$[b]
Attained age (years)			
5–9	0.1	3.9	0.98
10–19	3.0	10.0	0.94
20–29	7.8	14.2	0.80
30–39	12.1	9.9	0.57
40–49	25.2	11.8	0.42
50–59	32.9	11.1	0.41
60–69	55.4	19.6	0.41
70+	70.5	22.5	0.38
Calendar year			
1950–1960	40.1	41.8	0.67
1961–1970	34.9	20.2	0.49
1971–1980	41.3	13.4	0.39
1981–1990	44.9	15.0	0.41
1991–2000	45.7	12.6	0.34
Marrow dose (Gy)			
<0.005	99.1	0.2	—[c]
0.005–<0.1	64.8	5.3	0.08
0.1–<0.5	28.1	19.5	0.41
0.5–<1	8.4	19.5	0.70
1–<2	4.8	26.7	0.85
2+	1.7	31.8	0.95
Total	206.9	103.1	0.49

[a] Estimates of background and excess cases are based on ERR models shown in Table 3.
[b] Attributable fraction among those exposed to >0.005 Gy; $AF_{0.005}$ is the excess number of cases among those exposed to >0.005 Gy divided by the fitted number of cases among those exposed to >0.005 Gy.
[c] No value for $AF_{0.005}$ is shown for those exposed to <0.005 Gy.

The effect of age at exposure was parsimoniously modeled using the continuous term e'; the effect of time since exposure was modeled with a cubic spline function of t. It was found necessary to allow the effect of time since exposure to vary with age at exposure; a model with knots at 15, 30 and 45 years was not well estimated (i.e., did not converge); however, a reduced model with knots at 30 and 45 years after exposure fitted these data well. The terms for the main effect of time since exposure, $\delta_1 - \delta_5$, were not retained in this model because they contributed little to the model fit (LRT = 4.9, 5 *df*, $P = 0.42$), leading to a model of the form

$$ERR(d,e,t) = (\theta d^2)\exp\left[\gamma e' + \phi_1 e' t + \phi_2 e' t^2 + \phi_3 e' t^3 + \phi_5 e'(t-30)_+^3 + \phi_6 e'(t-45)_+^3\right].$$

There was no evidence of effect modification by sex (LRT = 0.0, 1 *df*; $P = 0.89$), nor was there evidence of a significant difference in the dose–response association between Hiroshima and Nagasaki survivors (LRT = 0.6, 1 *df*, $P = 0.43$). Table 3 reports the parameter estimates for the final model for AML. The parameter estimate $\hat{\theta}$ describes the quadratic dose–response function, $\hat{\gamma}$ describes the main effect of age at exposure, and $\hat{\phi}_1$, $\hat{\phi}_2$, $\hat{\phi}_3$, $\hat{\phi}_5$ and $\hat{\phi}_6$ describe the effect of time since exposure among those <30 years of age ATB.

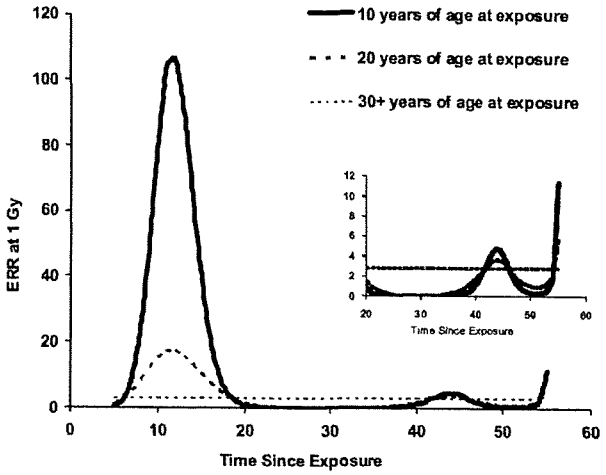

FIG. 2. Predicted ERR at 1 Gy for AML as a function of age at exposure and time since exposure. Inset provides an expanded view of ERR estimates for the period 20 or more years after exposure.

Figure 2 shows the predicted ERR at 1 Gy for AML as a function of time since exposure for people exposed at ages 10, 20 and 30+ years. The predicted ERR at 1 Gy for AML is quite large, particularly at young attained ages. Given the low baseline rate of AML at young attained ages, despite the large ERR/Gy, this corresponds to relatively small numbers of radiation-associated excess cases in this study population. Table 5 reports the estimated numbers of background and excess deaths due to AML. Approximately 38 of the 124 AML deaths were predicted to be excess cases attributed to radiation exposure under the fitted model. No deaths due to AML were observed at attained ages 5–9 years; the $AF_{0.005\ Gy}$ was near unity at attained ages 10–19 years. The $AF_{0.005\ Gy}$ was largest in the period 1950–1960, and, in the most recent decade of follow-up (1991–2000), the $AF_{0.005\ Gy}$ for AML was 0.36. The model-based time-averaged $AF_{0.005\ Gy}$ is 0.42, and the corresponding EAR estimate is 0.9 cases per 10^4 PY Gy.

Chronic Myeloid Leukemia

There were 58 deaths due to CML. Table 2 reports estimated rate ratios for mortality due to CML by categories of bone marrow dose, with people who had doses <0.005 Gy serving as the reference category. Estimated rate ratios increased in magnitude in each successively higher estimated dose category. The estimated dose–response association, derived using a linear

TABLE 5
Predicted Number of Background[a] Deaths, Excess Deaths, and the Attributable Fraction of Deaths due to AML, CML and ALL among those Exposed to >0.005 Gy ($AF_{0.005}$)[b]

	AML			CML			ALL		
	Fitted background	Fitted excess	$AF_{0.005}$[b]	Fitted background	Fitted excess	$AF_{0.005}$	Fitted background	Fitted excess	$AF_{0.005}$
Attained age									
5–9	0.0	0.0	n.d.	0.5	0.5	0.55	0.6	0.4	0.42
10–19	1.1	2.9	0.97	1.1	0.9	0.58	1.3	0.7	0.43
20–29	1.8	4.2	0.87	1.4	1.6	0.60	0.0	0.0	n.d.[c]
30–39	5.6	2.4	0.38	3.6	3.4	0.59	0.0	0.0	n.d.
40–49	12.2	3.8	0.31	4.4	5.6	0.60	2.1	0.9	0.45
50–59	12.0	4.0	0.37	2.8	2.2	0.60	1.6	0.4	0.47
60–69	21.3	7.7	0.39	11.7	7.3	0.59	4.8	2.2	0.47
70+	32.4	12.6	0.40	7.3	3.7	0.56	2.7	1.3	0.48
Calendar year									
1950–1960	13.7	12.0	0.68	8.2	9.4	0.60	2.2	1.3	0.42
1961–1970	13.5	6.8	0.41	6.5	5.7	0.60	1.4	0.6	0.46
1971–1980	17.3	3.8	0.26	8.5	5.5	0.58	3.4	1.1	0.47
1981–1990	20.9	8.0	0.40	6.5	3.7	0.58	2.7	1.3	0.47
1991–2000	21.0	7.1	0.36	3.1	1.0	0.55	3.5	1.5	0.48
Marrow dose									
<0.005	35.3	0.0	—[d]	15.1	0.1	–	6.2	0.0	–
0.005–<0.1	30.6	0.1	0.00	10.6	2.1	0.17	4.2	0.5	0.11
0.1–<0.5	13.5	2.6	0.16	4.8	7.2	0.60	1.8	1.6	0.46
0.5–<1	4.0	5.9	0.60	1.2	5.5	0.82	0.5	1.3	0.72
1–<2	2.1	11.9	0.85	0.7	5.8	0.90	0.2	1.3	0.84
2+	0.8	17.1	0.95	0.3	4.6	0.94	0.1	1.2	0.91
Total	86.4	37.7	0.42	32.7	25.3	0.59	13.1	5.9	0.46

[a] Estimates of background and excess cases are based on ERR models shown in Table 3.
[b] Attributable fraction among those exposed to >0.005 Gy; $AF_{0.005}$ is the excess number of cases among those exposed to >0.005 Gy divided by the fitted number of cases among those exposed to >0.005 Gy.
[c] Not determined; the fitted number of cases among those exposed to >0.005 Gy was zero.
[d] No value for $AF_{0.005}$ is shown for those exposed to <0.005 Gy.

ERR model without effect modification, was significant (LRT = 31.9, 1 *df*, $P < 0.001$). A comparison of a model with a purely linear dose–response function to a model in which the dose–response association is linear-quadratic indicates that inclusion of a quadratic term contributes little to the goodness of fit of the model (LRT = 1.3, 1 *df*, $P = 0.3$). The analyses of effect modification, described below, were based upon a model with a linear dose–response function.

The goodness of model fit changed minimally when age at exposure entered the model as a categorical term or as the continuous term e'. Neither inclusion of a loglinear subterm for time since exposure nor inclusion of a spline function for time since exposure contributed substantially to the model fit (LRT = 1.9, 1 *df* $P = 0.16$ and LRT = 3.4, 2 *df*, $P = 0.19$). The final preferred model was a time-constant linear ERR model. There was minimal evidence of heterogeneity in the dose–response association by sex (LRT = 1.5, 1 *df* $P = 0.22$) or by city (LRT = 0.5, 1 *df* $P = 0.47$). Table 3 reports the parameter estimate for the final model for CML. The model includes a single term, β, which describes the time-constant linear dose–response function.

The predicted ERR/Gy for CML is a time-constant function and thus there is no need for a figure illustrating the pattern of ERR/Gy as a function of time since exposure and age at exposure. Approximately 25 of the 58 CML deaths were predicted to be excess CML deaths associated with radiation exposure (Table 5); the model-based time-averaged $AF_{0.005\ Gy}$ is 0.59. The corresponding time-averaged EAR estimate is 0.6 cases per 10^4 PY Gy.

Acute Lymphocytic Leukemia

There are 19 deaths due to ALL in the study cohort, with only two deaths observed among cohort members from Nagasaki. Table 2 reports estimated rate ratios for mortality due to ALL by categories of bone marrow dose, with people who had doses <0.005 Gy serving as the reference category. Estimated rate ratios were greater than unity in each estimated dose category; the estimated rate ratio was slightly smaller in magnitude for those with estimated doses 0.1–0.5 Gy than for those with estimated doses of 0.005–0.1 Gy. The estimated dose–response association, derived using a linear ERR model without effect modification, was significant (LRT

= 7.7, 1 *df*, $P = 0.006$). The dose–response association for ALL can be adequately described by a linear model; a comparison of a model with a purely linear dose–response function to a model in which the association is linear-quadratic indicates that inclusion of a quadratic term contributes very little to the model fit (LRT = 0.06, 1 *df*, $P < 0.50$). The analyses of effect modification, described below, were based upon a model with a linear dose–response function.

Neither inclusion of a loglinear subterm for age at exposure nor inclusion of indicator terms for categories of age at exposure contributed substantially to the model fit (LRT = 0.2, 1 *df* and LRT = , 1 *df*, respectively). Similarly, neither inclusion of a loglinear subterm for time since exposure nor inclusion of a spline function for time since exposure contributed substantially to the model fit (LRT = 1.9, 1 *df* $P = 0.16$ and LRT = 3.4, 2 *df*, $P = 0.19$). The final preferred model was a time-constant linear ERR model. City differences in dose effects could not be estimated since only two cases of ALL were observed among Nagasaki bomb survivors. There is no evidence of difference by sex in the dose–response association when evaluated via the time-constant model (LRT = 0.0, 1 *df*, $P < 0.5$). Table 3 reports the parameter estimate for the final model for ALL; the estimate, $\hat{\beta}$, describes the time-constant linear dose–response function.

The predicted ERR/Gy for ALL is a time-constant function and there is therefore no need for a figure illustrating the pattern of ERR/Gy as a function of time since exposure and age at exposure. The model-based time-averaged $AF_{0.005\ Gy}$ is 0.46 for ALL, and the time-averaged EAR estimate is 0.1 cases per 10^4 PY Gy.

Adult T-Cell Leukemia

Table 2 reports estimated rate ratios for mortality due to ATL by categories of bone marrow dose, with people who had doses <0.005 Gy serving as the reference category. People in the highest three dose categories were coalesced into a single dose group defined as 0.5+ Gy, since no deaths due to ATL were observed among those with estimated doses greater than or equal to 1 Gy. The estimated rate ratio was greater than unity among people with estimated doses of 0.005–0.1 Gy, although the associated confidence interval was relatively wide. The estimated rate ratios for the other dose categories were less than unity. The estimated dose–response association, derived using a linear ERR model without effect modification, was not significant (LRT = 0.3, 1 *df*, $P < 0.50$). The point estimate for the ERR was negative, and the upper 90% confidence bound was 1.78.

Inclusion of a loglinear subterm for age at exposure contributed little to the model (LRT = 0.0, 1 *df*, $P < 0.5$); similarly, inclusion of a subterm for time since exposure led to essentially no improvement in model fit (LRT = 0.0, 1 *df*, $P < 0.5$). City differences in dose effects could not be estimated since only one case of ATL was observed among Hiroshima bomb survivors. There is no evidence of heterogeneity by sex in the dose–response association (LRT = 0.2, 1 *df*, $P < 0.5$). Replication of analyses of ATL restricted to Nagasaki survivors led to very similar results (results not shown). As indicated in Table 3, under the final model for ATL the ERR is not a function of dose; therefore, a detailed description of the radiation-associated excess risk is not shown.

DISCUSSION

This study examines leukemia mortality among members of the LSS during the period October 1, 1950–December 31, 2000 in relation to DS02 estimated bone marrow doses. These analyses provide evidence regarding the magnitude and shape of the radiation dose–leukemia mortality association by type of leukemia.

Although this is the first comprehensive analysis of leukemia mortality in the LSS by type of leukemia, previous reports have described type-specific analyses of leukemia incidence in the LSS. Preston *et al.* examined cancer incidence in the period 1950–1987, noting positive associations between radiation dose and risk of AML, CML and ALL (*6*). In this paper the preferred models for ALL and CML involve time-constant linear dose–response functions. Preston *et al.*, while developing EAR models rather than ERR models, similarly concluded that the best-fitting model was linear for ALL and CML. Consistent with previous analyses by Preston *et al.*, we observed no association between radiation dose and mortality due to ATL. Our preferred model for AML is purely quadratic while our preferred model for total leukemia is linear-quadratic. Preston *et al.* employed a linear-quadratic model for AML, reporting a time-averaged, model-based EAR = 1.1 cases per 10^4 PY Sv. This summary statistic does not fully describe the nature of the radiation risk in this population; however, it does provide one basis for comparison between analyses. The value reported by Preston *et al.* is similar to the value reported in the current paper (EAR = 0.9 cases per 10^4 PY Gy). For CML, Preston *et al.* reported a time-averaged, model-based EAR = 0.9 cases per 10^4 PY Sv; again, this is similar to the EAR for CML reported in the current paper. For leukemia of all types, Preston *et al.* reported a time-averaged, model-based EAR = 2.7 cases per 10^4 PY Sv; in the current paper the corresponding value is EAR = 2.4 cases per 10^4 PY Gy. Perhaps the most notable difference in the summary statistics between the report by Preston *et al.* and the current report is for ALL. Preston *et al.* reported a time-averaged, model-based EAR = 0.6 cases per 10^4 PY Sv; in the current

paper the corresponding values for ALL is EAR = 0.1 cases per 10^4 PY Gy. The aim of this paper was to report on the risk of radiation-related mortality by type of leukemia among the Japanese atomic bomb survivors in LSS. The non-monotonic dose-time-response patterns for all leukemias, and AML, could not be modeled for other leukemia subtypes given the relative rarity of events. We have not evaluated statistical tests of interaction between model parameters for dose-time-response associations and disease entities (i.e., modification of dose-time-response associations by disease type), as might be obtained by joint modeling of disease subtypes.

Since these analyses rely upon death certificate information for classifying decedents with respect to type of leukemia, outcome misclassification is a reasonable concern. We noted that, relative to the incidence analysis by Preston *et al.* (*6*), the current study includes a smaller proportion of events attributed to ALL, suggesting misclassification of the underlying cause of death information for some ALL deaths. Misclassification is likely to be particularly serious in the early years of follow-up, which are of considerable interest for ALL.

We found that classification of ATL was particularly problematic; prior to 1980 ATL was not a condition recorded on the death certificate (Table 1). The marked difference between the number of ATL deaths observed in Nagasaki and the number observed in Hiroshima is consistent with prior findings that ATL occurs at a low rate in Nagasaki and is virtually nonexistent in Hiroshima. The difference has been attributed to differences between cities in the prevalence of HTLV-1 infection (*21*). While we did not observe a positive association between ionizing radiation dose and ATL in these analyses, an obvious limitation of this study was the absence of deaths attributed to ATL until the period 35 or more years after exposure.

In the analysis of CML incidence reported by Preston *et al.* (*6*), several findings are noteworthy. Preston *et al.* modeled the excess absolute risk (EAR) of CML, reporting a significant difference between the EARs for Hiroshima and Nagasaki. The magnitude of the city effect was roughly proportional to the city difference observed in background CML rates, suggesting that the difference in radiation effects between the two cities can be explained by differences in background rates. We modeled the relative, rather than absolute, risk of CML; consistent with Preston *et al.*'s observation, we found no evidence of a city difference in the radiation-CML association. Preston *et al.* noted that the EAR for women remained relatively constant with time since exposure whereas the EAR for men decreased with time since exposure. In this paper, our preferred model for CML is time constant because neither age at exposure nor time since exposure contributed substantially to the fit of the ERR model for CML mortality.

The LSS lacks direct measurement of survivors' radiation doses. Substantial effort has been devoted to estimation of survivors' doses based on air dose curves, attenuation curves for different shielding situations, and self-reported information on location and shielding conditions at the time of the bombing. Nonetheless, in some instances, the shielding and location information is of dubious validity, and prior work has raised concerns about the accuracy of some survivors' dose estimates, particularly for those in locations with complex shielding conditions (*9*). Potentially illustrative of such problems are concerns regarding overestimation of radiation doses for a group of 652 Nagasaki factory workers (*9*). Four deaths due to leukemia were observed among these factory workers, and the average estimated marrow dose for those decedents was 0.94 Gy. While overall results are minimally affected by their inclusion, a likelihood ratio test provides somewhat less evidence of heterogeneity in the dose–response function by city upon their exclusion (LRT = 5.2, 1 *df*). Another potential concern is our assumption about the relative biological effectiveness of the neutron component of these survivors' doses. We have assumed a relative biological effectiveness for neutrons of 10. A different assumption about the relative biological effectiveness of neutrons would affect the classification of survivors with respect to dose. Some atomic bomb survivors were exposed to radiation from fallout and/or from neutron activation of ground and structures (*1*). We did not directly assess confounding by fallout or residual radiation, and consequently this raises concerns about errors in exposure classification. Available data suggest that people near the hypocenters tended to have lower doses from fallout than some people in more distal locations, particularly those people who were in an area of Nagasaki about 3 kilometers from the hypocenter[2] (*1*).

In addition to accuracy in the measurement of exposure and outcomes, accurate estimation of radiation dose–leukemia mortality associations requires the absence of confounding. Unlike a study in which exposure is randomized by design, in the LSS doses were non-randomly distributed through the populations of the bombed cities. Prior research suggests that LSS cohort members, particularly men, who were in the towns at the time of the bombings tended to be more highly educated and less likely to work in occupations such as agriculture and fishing than men who were at distal locations at the time of the bombings (*22, 23*). If risk factors for leukemia that were associated with education, residence or occupation were correlated with dose, then the true effect of radiation may be obscured or exaggerated. In the current analyses we have adjusted for differences in background mortality rates between proximal and distal

[2] Frequently Asked Questions, Radiation Effects Research Foundation. Available online at http://www.rerf.or.jp.

survivors. We observed differences in baseline leukemia mortality rates between proximal and distal survivors, particularly in the first decade after the bombings. Adjustment for proximal or distal location ATB affected the estimates of radiation dose–leukemia mortality associations (Appendix Table A1). Differences in baseline mortality rates by location at time of bombing may also reflect selective survival among proximal survivors. Adjustment for baseline differences in mortality rates between proximal and distal survivors minimizes problems of confounding by proximal or distal location but does not address concerns that survivors of the atomic bombings may be a select group of people who are relatively less susceptibility to radiation-induced leukemia than the general population (*24*). While not easily evaluated empirically, theoretical work on the potential for bias on solid cancer risk estimates, considering a range of values for the magnitude of dose-related selective survival, suggested that the potential bias under the scenarios considered was modest (*25*).

In these analyses the magnitude of the radiation dose–leukemia mortality association was approximately threefold larger for Hiroshima survivors than for Nagasaki survivors. This could reflect differences between cities in co-exposures or other factors influencing susceptibility to radiation-induced leukemia, differences in exposure conditions, or differences by city in the accuracy of exposure or outcome classification. The shape of the dose–response association also appears to differ by city. The linear-quadratic shape of the dose response for leukemia in the LSS has been given substantial attention in the literature. Interpretations for a linear-quadratic dose–response function have been posited in the context of the theory of dual action of ionizing radiation and have played an important role in discussions of risk projections to low-dose (< 0.1 Gy) or low-dose-rate exposures. Evidence of heterogeneity by city in the shape of the radiation dose–leukemia mortality association suggests that caution is warranted when attributing a biological interpretation to the parametric form of this dose–response association.

Comparison to the National Academy of Science's Biological Effects of Ionizing Radiation (BEIR) VII Report

The findings of this mortality analysis complement the BEIR VII report, which examined leukemia mortality in the same cohort of LSS members followed over the same period (1950–2000) (*8*). The current report presents findings for specific types of leukemia. There are, in addition, a number of differences between the approach used in this report and that taken by the BEIR VII committee. While spanning the same period of follow-up, this analysis includes more deaths due to leukemia than the analysis in the BEIR VII report. The BEIR VII analysis of leukemia mortality in the LSS included some but not all deaths due to ATL; that analysis included only those deaths due to ATL that were coded to the 10th revision of the ICD, while we have included all deaths for which ATL was noted as the underlying cause of death (see Materials and Methods).

Unlike the recent BEIR VII report, our preferred model for the ERR of leukemia does not allow for sex differences in the radiation dose–mortality association (*8*). There was no evidence of such heterogeneity in our analyses, nor does such a product term appear to be necessary in the BEIR VII leukemia model. In the current analysis, control for potential confounders was achieved through background stratification, while the recent BEIR analyses employed a parametric model for baseline rates. In addition, we adjusted for confounding of the radiation dose–leukemia mortality association by proximal or distal location, a covariate not included in the BEIR VII analysis (see Appendix). Furthermore, we used a cubic spline function to model the modifying effect of time since exposure in analyses of leukemia of all types and acute myeloid leukemia. Our preferred models for mortality due to ALL and CML are simple time-constant ERR functions; the numbers of deaths due to these types of leukemia were quite small, and there was relatively little statistical support for fitting of more complex time-varying ERR models for those outcomes.

Although we have taken a somewhat different analytical approach from that taken in the BEIR VII report, we can compare predictions of the ERR/Gy for leukemia of all types to the values reported in the BEIR VII report. One complication of such a comparison is an apparently erroneous figure in the BEIR VII report. Figure 12-2 of the BEIR VII report was intended to illustrate the predicted ERR/Gy for leukemia of all types. However, the ERRs shown in that figure are roughly half the magnitude of the correct values obtained by direct calculation using the Committee's reported model coefficients. Appendix Fig. A4 presents a correct illustration of the ERR/Gy for leukemia calculated using the BEIR VII Committee's model coefficients; also shown are the values derived using the coefficient estimates for the preferred model in this paper.

Conclusion

Members of the LSS cohort have been followed for over half a century. For contemporary Japanese atomic bomb survivors, an important question is whether leukemia risk diminished entirely within the first decades after the bombings, or whether excess risk of leukemia continues to persist. These analyses suggest that the variation in ERR/Gy with time since exposure appears to diverge from the monotonic decay function posited in prior analyses of leukemia mortality and incidence (*8*). Under the model for leukemia that was fitted in the

current paper, in the most recent decade of observation (1991–2000), 34% of the deaths due to leukemia observed among members of the LSS with doses over 0.005 Gy were estimated to be radiation-associated excess deaths (Table 4). The majority of the predicted excess leukemia deaths in this period are due to AML (Table 4). While regression models that incorporate spline functions are empirical rather than biological models for analysis of epidemiological data, the temporal variation in the ERR of leukemia is interesting to consider in terms of biological models of radiation-related leukemia. Early onset of leukemia (or leukemia with short latency) may have occurred among those who are predisposed by the presence of spontaneously arising clonally expanded preleukemic cells (*26*). In contrast, late-onset leukemia, observed decades after irradiation, may be less related to clonal expansion of preleukemic cells and more related to induction of cancers by contributing to one step in the malignant transformation of cells (similar to the pattern observed for solid cancers).

The persistent evidence of excess leukemia among Japanese atomic bomb survivors underscores the importance of the LSS to understanding the long-term health effects of exposure to ionizing radiation. These observations should be of interest to contemporary A-bomb survivors and their caregivers and more generally to those interested in the human health effects of nuclear weapons and other sources of ionizing radiation exposures.

APPENDIX

There are several differences between the analysis of leukemia mortality in the current paper and the analysis of leukemia mortality reported in the National Academy of Science's BEIR VII report (*8*). The BEIR VII analysis of leukemia mortality in the LSS included only those deaths due to ATL that were coded to the 10th revision of the ICD while the current paper included all deaths for which ATL was noted as the underlying cause of death. In the current paper we adjusted for baseline differences in mortality by background stratification. We also allowed for mortality differences between proximal and distal atomic bomb survivors. In addition, in the current paper we employed a cubic spline model to describe temporal variation in the excess relative rate of leukemia. In the text below we discuss some of these differences.

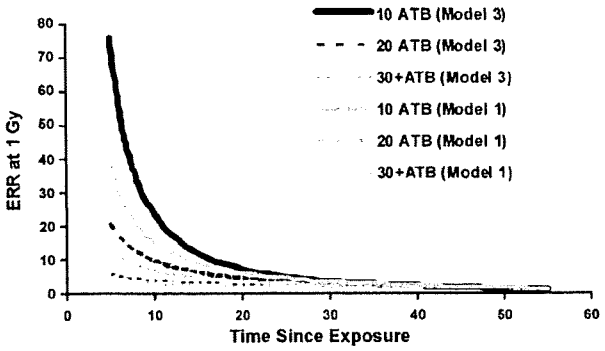

FIG. A1. Estimated sex-averaged excess relative rate of leukemia mortality as a function of bone marrow dose (in weighted Gy) among A-bomb survivors in the LSS exposed at ages 10 years, 20 years and 30+ years at time of bombing (ATB). Results shown for two models. Model 1 adjusts for baseline leukemia mortality rates using a loglinear subterm of the linear relative rate model that includes terms for city, sex and for each sex, a linear-quadratic spline function of log *age*, with a knot at age 70 years, and a linear-quadratic function of birth year. Model 3 employs background stratification on sex, city, attained age, age at exposure, and proximal or distal location.

Adjustment for Baseline Factors

The BEIR VII Committee's preferred ERR model for leukemia is of the form $ERR(d,s,e,t) = \beta_s(d + \theta d^2)\exp[\gamma e' + \delta \log(t/25) + \phi e' \log(t/25)]$, where d is the dose to the bone marrow (in weighted Gy), e is age at exposure (in years), e' is $(e - 30)/10$ for $e < 30$ and zero otherwise, and t is time since exposure (in years). The values for

TABLE A1
Estimated Model Coefficients for the Association between Bone Marrow Dose and Leukemia Mortality among A-Bomb Survivors in the LSS under an Excess Relative Rate Model of the Form
$ERR(d, c, s, e, t) = \beta_s(d + \theta d^2)\exp[\gamma e' + \delta \log(t/25) + \phi e' \log(t/25)]$

Model	Model 1[a]	Model 2[b]	Model 3[c]
Parameter	Estimate (95% CI)	Estimate (90% CI)	Estimate (90% CI)
β_M	1.1 (0.1, 2.6)	1.4 (0.3, 3.4)	1.5 (0.2, 3.9)
β_F	1.2 (0.1, 2.9)	1.6 (0.3, 3.8)	1.6 (0.3, 4.0)
γ	−0.40 (−0.78, 0.00)	−0.39 (−0.77, −0.00)	−0.32 (−0.77, 0.16)
δ	−0.48 (−1.10, 0.18)	−0.47 (−1.08, 0.17)	−0.47 (−1.29, 0.34)
ϕ	0.42 (−0.05, 0.96)	0.41 (−0.05, 0.94)	0.60 (−0.03, 1.38)
θ	0.88 (0.16, 15.27)	0.66 (0.10, 5.32)	0.75 (0.13, 6.72)
Residual deviation	2255.22	2250.10	1560.32
df	33200	33198	32133

Note. Results of fitting three models that employ different approaches to adjusting for baseline leukemia mortality rates.

[a] Model 1 adjusts for baseline leukemia mortality rates using a loglinear subterm of the linear relative rate model that includes terms for city, sex, and, for each sex, a linear-quadratic spline function of the natural log of attained age, with a knot at age 70 years, and a linear-quadratic function of birth year.

[b] Model 2 specifies the same parametric baseline model as Model 1 with the exception that the binary indicator variable for city was replaced by a four-level variable that indicated proximal compared to distal location ATB in each city.

[c] Model 3 employs background stratification on sex, city, attained age, age at exposure, and proximal or distal location.

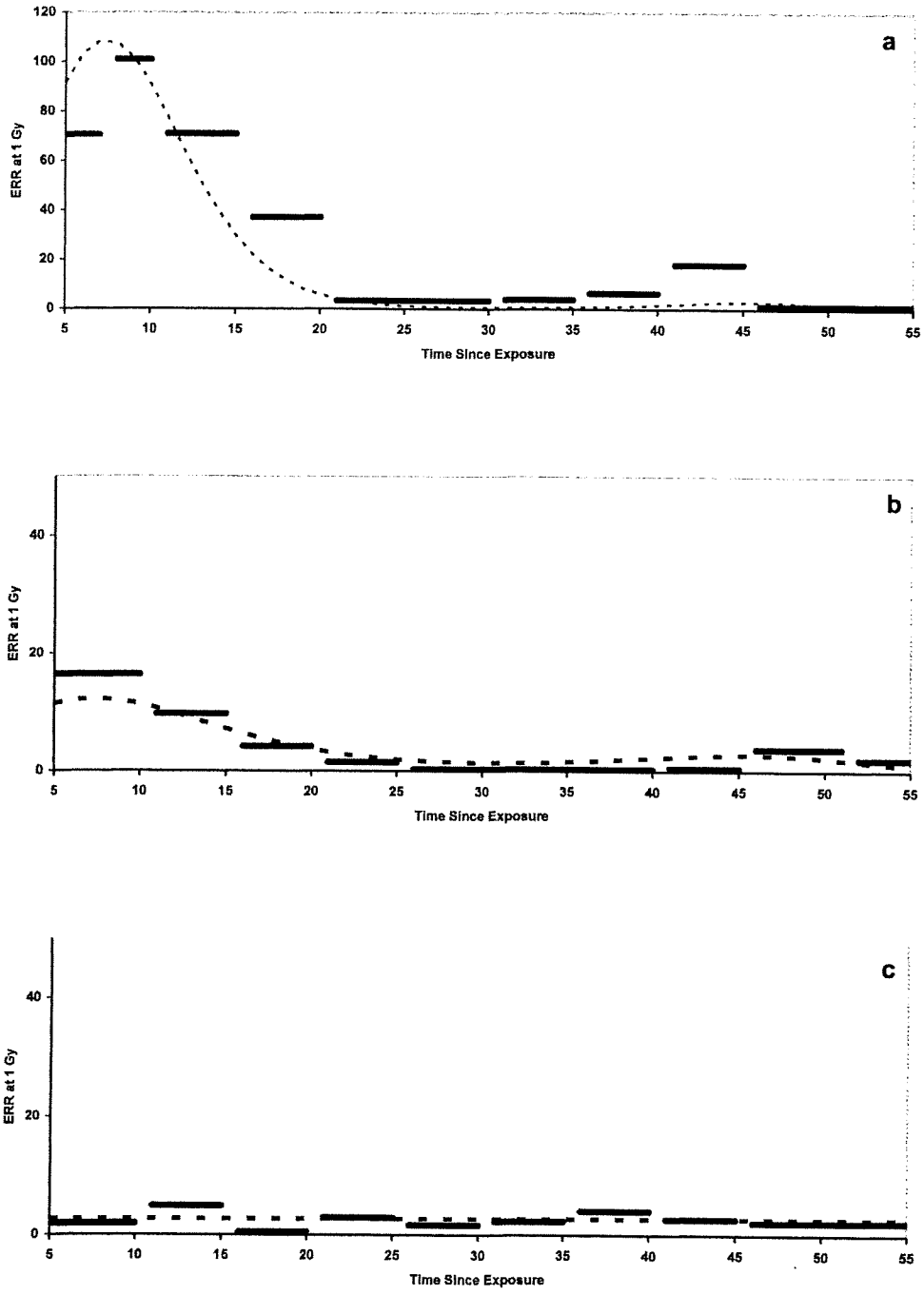

FIG. A2. Evaluation of modification of association between radiation and death due to leukemia of all types by age at exposure and time since exposure. Piecewise constant estimates of the excess relative risk at 1 Gy for people exposed at ages (panel a) <10, (panel b) 10–<30, and (panel c) 30+ years. Dashed lines indicate fitted cubic spline model.

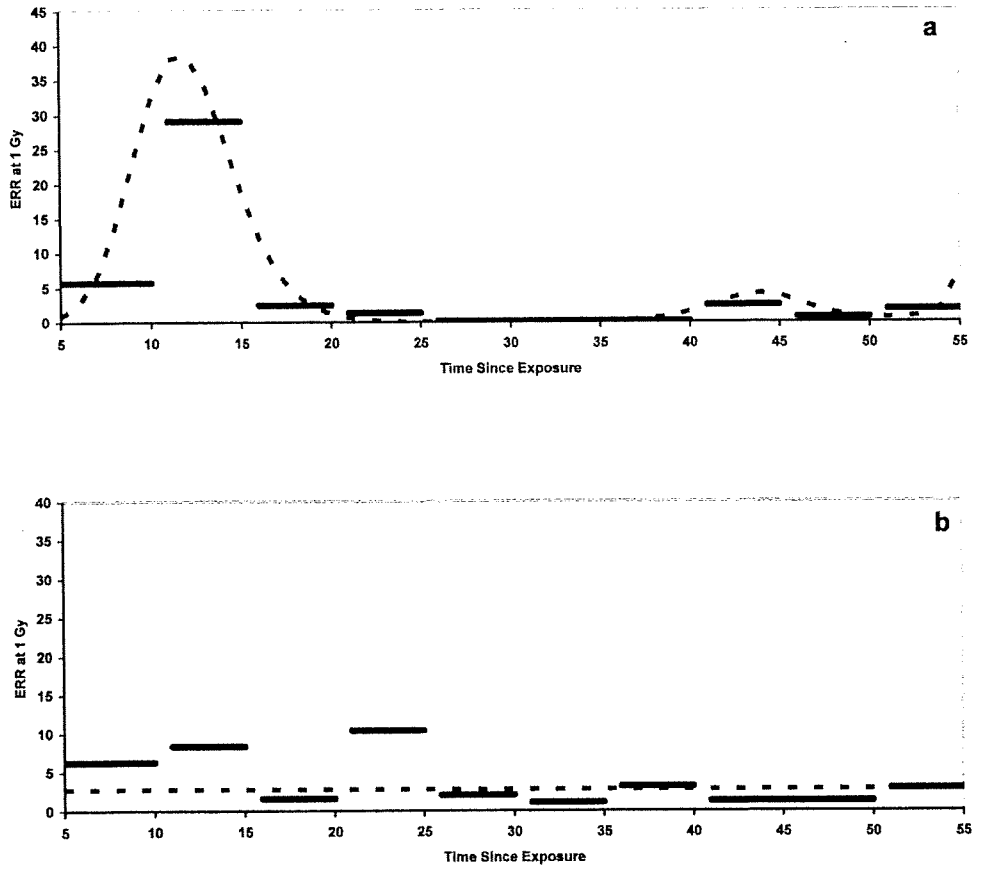

FIG. A3. Evaluation of modification of association between radiation and death due to AML by age at exposure and time since exposure. Piecewise constant estimates of the excess relative risk at 1 Gy for people exposed at ages (panel a) <30 and (panel b) 30+ years. Dashed lines indicate fitted cubic spline model.

these model parameters as provided in the BEIR VII report are as follows: $\beta_M = 1.1$ (95% CI: 0.1, 2.6), $\beta_F = 1.2$ (95% CI: 0.1, 2.9), $\gamma = -0.40$ (95% CI: −0.78, 0.0), $\delta = -0.48$ (95% CI: −1.1, 0.2), $\phi = 0.42$ (95% CI: 0.0, 0.96), $\theta = 0.87$ (95% CI: 0.16, 15).

Table A1 reports estimates of the parameters for the BEIR VII Committee's preferred ERR model for leukemia as obtained using three regression analyses; for comparability with the BEIR VII report, 95% confidence intervals are reported for these parameter estimates. To achieve comparability in the definition of the mortality outcome, the analysis reported in Table A1 is based upon the data set used by Preston *et al.* (*9*), which encompasses the same cohort of LSS members examined in the current paper with follow-up spanning the same period. However, the category of all leukemia deaths was defined by Preston *et al.* (*9*) to include only those deaths due to ATL that were coded to the 10th edition of the ICD. Model 1 specifies a parametric baseline model for the rate of leukemia that includes terms for city, sex and, for each sex, a linear-quadratic spline function of log of attained age, with a knot at age 70 years, and a linear-quadratic function of birth year. The parameter estimates obtained using Model 1 are equivalent to those reported in the BEIR VII report. Model 2 specifies the same parametric baseline model; however, the binary indicator variable for city was replaced by a four-level variable that indicated proximal or distal location ATB in each city. Evidence of confounding by proximal or distal location ATB is suggested by the change in the estimates of the parameters for the ERR model upon adjustment for this factor. Model 3 employs background stratification on sex (*s*), city (*c*), attained age (*a*), age at exposure (*e*), and proximal or distal location (*l*). Stratification allows the effect of proximal or distal location to vary over time, as a consequence of its cross-classification with attained age and age at exposure. Background stratification on *s*, *c*, *a*, *e* and *l* was employed in the current paper to obtain control for confounding by these covariates. Figure A1 illustrates the estimates of the age–time patterns of ERR at 1 Gy obtained with Model 1 and with Model 3.

Cubic Spline Models

Use of a cubic spline function to model effect modification by time since exposure is a departure from the approach employed in previous analyses of leukemia mortality among LSS survivors (*8*, *19*). However, neither a model with a monotonic function of t nor $\log(t)$ fits these data as well (LRT = 9.3, 2.*df*, $P = 0.01$ and LRT = 6.9, 2 *df*, $P = 0.03$, respectively). Regression model development involves a balance between over-smoothing, thereby obscuring potentially important patterns in the data, and over-fitting, which may result in model parameters that are highly sensitive to minor perturbations in the data. Cubic spline functions are attractive because they accommodate a wide variety of functional forms; nonetheless, there are limitations to spline functions, such as a tendency for instability in the tails of the fitted function. Such concerns were addressed in part by assessing the fit of our model to the data by reference to model estimates of temporal variation in the

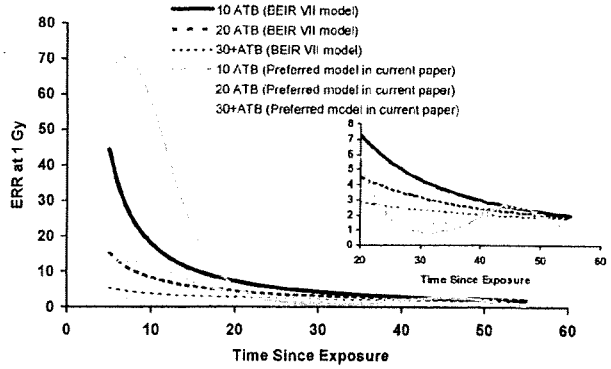

FIG. A4. Estimated excess relative rate of leukemia mortality as a function of bone marrow dose (in weighted Gy) among A-bomb survivors in the LSS exposed at ages 10 years, 20 years and 30+ years at time of bombing (ATB). Results shown for the BEIR VII model (sex-averaged) and the preferred model in the current paper (city-averaged). The BEIR VII model is the preferred excess relative rate model for leukemia reported in the National Academy of Science's BEIR VII report. The preferred model in the current paper is the model for leukemia: all types shown in Table 3.

ERR/Gy obtained with a piecewise constant model for time since exposure. Separate analyses were conducted for survivors exposed at ages 0–9 years, 10–29 years and 30+ years considering death due to leukemia of all types (Fig. A2) and death due to AML (Fig. A3). The horizontal line segments in each figure illustrate the estimates of the ERR at 1 Gy as a piecewise constant function of time since exposure; the dashed line in each figure illustrates the fitted cubic spline model, plotted at the mean age ATB of the decedents included in each analysis.

Figure A4 illustrates the ERR/Gy for leukemia derived using the coefficient estimates for the preferred model in this paper and the values calculated using the BEIR VII Committee's model coefficients.

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RESEARCH

Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003

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ABSTRACT

Objective To investigate the degree to which ionising radiation confers risk of mortality from heart disease and stroke.

Design Prospective cohort study with more than 50 years of follow-up.

Setting Atomic bomb survivors in Hiroshima and Nagasaki, Japan.

Participants 86 611 Life Span Study cohort members with individually estimated radiation doses from 0 to >3 Gy (86% received <0.2 Gy).

Main outcome measures Mortality from stroke or heart disease as the underlying cause of death and dose-response relations with atomic bomb radiation.

Results About 9600 participants died of stroke and 8400 died of heart disease between 1950 and 2003. For stroke, the estimated excess relative risk per gray was 9% (95% confidence interval 1% to 17%, P=0.02) on the basis of a linear dose-response model, but an indication of possible upward curvature suggested relatively little risk at low doses. For heart disease, the estimated excess relative risk per gray was 14% (6% to 23%, P<0.001); a linear model provided the best fit, suggesting excess risk even at lower doses. However, the dose-response effect over the restricted dose range of 0 to 0.5 Gy was not significant. Prospective data on smoking, alcohol intake, education, occupation, obesity, and diabetes had almost no impact on the radiation risk estimates for either stroke or heart disease, and misdiagnosis of cancers as circulatory diseases could not account for the associations seen.

Conclusion Doses above 0.5 Gy are associated with an elevated risk of both stroke and heart disease, but the degree of risk at lower doses is unclear. Stroke and heart disease together account for about one third as many radiation associated excess deaths as do cancers among atomic bomb survivors.

INTRODUCTION

The effects of radiation on incidence of or mortality from circulatory disease have large implications for public health, especially if effects occur at doses under 1 Gy. Given that the frequency of multiple computed tomography scans of the head or chest and of interventional radiographic procedures is increasing rapidly, information on whether these may confer risk for subsequent stroke or heart disease is essential.

Several studies, including randomised controlled trials, have found that high doses of radiation to the heart from radiotherapy for Hodgkin's disease or breast cancer cause an excess of deaths from heart disease in later years,[1-4] and other studies have suggested that radiotherapy for Hodgkin's disease, childhood leukaemia or brain tumours, and head and neck cancer increases the risk of stroke.[5-8] Several authors have suggested that lower doses from occupational, medical, and environmental exposures may be associated with excess mortality from circulatory disease,[9-14] although other studies have not found such low dose effects,[15-19] and information on doses and potential confounding lifestyle factors is limited in many of the studies of low doses. We examined the dose-response information on the risk of heart disease and stroke in the large Life Span Study cohort of atomic bomb survivors in Hiroshima and Nagasaki who have been followed up for 53 years, from 1950 to 2003.

METHODS

Study population

The Life Span Study cohort, defined on the basis of the Japanese national census in 1950 and special surveys between 1950 and 1953, consists of 86 611 atomic bomb survivors with estimated radiation doses. It includes a large proportion of the survivors who were within 2.5 km of the hypocentres at the time of the bombings and still resided in Hiroshima or Nagasaki in 1950, plus a random age and sex matched sample of people 2.5 to 10 km from the hypocentre who sustained small to negligible radiation doses.[20] This study population was of all ages and both sexes at the time of the bombings.

Individual doses have been carefully estimated using the recent improved DS02 dosimetry system,

primarily on the basis of people's location and shielding at the time of the atomic bomb.[21 22] We estimated risks by using weighted colon doses in gray (Gy) for all analyses. We used weighted doses, the sum of the γ dose plus 10 times the smaller neutron dose, to allow for the greater biological effectiveness of neutrons.

The follow-up of vital status took place from 1 October 1950 to the end of 2003 and was based on the nationwide obligatory family registration system (koseki) that documents mortality and is virtually 100% complete. Causes of death came from the official vital statistics death schedules based on the death certificates. Underlying and contributing causes of death were classified according to the ICD-7 (international classification of diseases, 7th revision) (for deaths in 1950-68), ICD-8 (in 1969-78), ICD-9 (in 1979-97), and ICD-10 (in 1998-2003). However, for the purposes of these analyses we converted them to ICD-9 codes 390-459 for all circulatory disease, 430-438 for stroke, and 393-429 (excluding 401, 403, and 405) for heart disease. We used only underlying causes of death in the primary analyses but examined underlying plus contributing causes in a subsidiary analysis.

Collection of covariate data and data from autopsy and tumour registry

A mail survey was sent to a defined sub-cohort of 51 965 Life Span Study cohort members in 1978. Information was obtained from 36 468 (response rate of 70%) on sociodemographic (education, type of occupation), lifestyle (smoking, alcohol intake), and health variables (obesity, diabetes mellitus), which enabled the evaluation of possible confounding by these variables. Between 1950 and 1985 autopsy data were also available on more than 1900 deaths that had an underlying cause of circulatory disease on the death certificate, which permitted evaluation of diagnostic accuracy. To identify pre-existing cases of cancer, we used the Hiroshima and Nagasaki tumour registries (available since 1958) and tissue registries (since 1974).

Statistical analysis

We based the analyses on a detailed summary table of the number of deaths and person years stratified by dose, city, sex, and five year intervals of age at exposure, attained age, and follow-up period. We divided participants into categories according to the weighted colon dose (in Gy=γ dose plus 10 times neutron dose): 0-, 0.005-, 0.02-, 0.04-, 0.06-, 0.08-, 0.1-, 0.125-, 0.15-, 0.175-, 0.2-, 0.25-, 0.3-, 0.5-, 0.75-, 1-, 1.25-, 1.5-, 1.75-, 2-, 2.5-, and ≥3. As described elsewhere, we truncated the colon doses to correspond to the 4 Gy shielded kerma level,[20] but this affected only 317 participants.

We used Poisson regression methods for grouped survival data to describe the dependence of risk on radiation dose and to evaluate the variation of the dose-response effects with respect to city, sex, age at exposure, time since exposure, and attained age,[23] essentially identical to the methods used previously to examine mortality from cancer in this cohort.[20] We used Epicure software for parameter estimation and tests,[24] and we based significance tests and 95% confidence intervals on likelihood profiles.

The primary models used here are excess relative risk (ERR) models of the form λ_0 (c,s,a,b) [1+ERR (d, e,s,a)], where λ_0 () is the baseline, or background death rate (that is, the rate for people with zero dose), which depended on city (c), sex (s), attained age (a), and birth year (b). The function ERR (d,e,s,a) describes the relative change in rates associated with dose (d), allowing for the effects of sex, age at exposure (e), and attained age. We examined effect modifiers by using models corresponding to those in Preston et al.[20 25] We examined both dose and dose squared terms to evaluate the degree of linearity or curvature in the dose-response forms. We also tested a linear threshold model. We used differences in maximum likelihood to compare nested models or the Akaike information criterion for non-nested models.[26] We evaluated a linear threshold model repeatedly for a wide range of possible values of a threshold dose (d_0), modelling the risk function ERR on doses d as $\beta(d-d_0)$ for $d>d_0$ or $d=0$ for $d\leq d_0$. We empirically determined the values yielding the maximum likelihood and 95% confidence bounds.

We examined the impact of the possible confounding factors of smoking (never, past, present <20/day, present ≥20/day), alcohol intake (regular, seldom/never), education (primary or less, secondary, college/university), occupation for household (professional/technical, clerical/sales, farmer/craftsman, transportation/service), obesity (body mass index <20, 20-24, ≥25), and diabetes (yes, no) on the estimates of radiation risk, including codes for missing information, for the Life Span Study participants included in the 1978 mail survey. We included Cox-type regression models fitted to the individual data, where radiation dose was modelled as a linear excess relative risk, and indicator variables for the potential confounders jointly in the models as conventional exponential relative risk terms by using the Peanuts program in Epicure.[24]

RESULTS

During follow-up, 19 054 deaths from circulatory disease occurred among the 86 611 Life Span Study members with DS02 dose available. Table 1 shows the numbers of participants and deaths from circulatory disease by age, sex, and radiation dose. The cohort covers a wide range of doses but is weighted towards low doses, which indicates that it has considerable capability to examine risks at low doses and to examine the shape of the dose-response curve. The deaths included 9622 from stroke, 8463 from heart disease, and 969 from other circulatory diseases. The excess relative risk per Gy for all circulatory disease based on the linear model over the full dose range was 11% (95% confidence interval 5% to 17%, P<0.001). This represents about 210 excess cases of death from circulatory disease associated with the exposure to radiation.

Table 1 | Number of participants and deaths from circulatory disease

Characteristics	No of people (n=86 611)	No of deaths			
		Circulatory disease (n=19 054)	Stroke (n=9 622)	Heart disease (n=8 463)	Other circulatory disease (n=969)
Sex:					
Male	35 687	7 607	3 958	3 261	388
Female	50 924	11 447	5 664	5 202	581
Age at atomic bomb exposure (years):					
0-9	17 833	428	176	238	14
10-19	17 563	951	404	508	39
20-29	10 891	1 551	652	831	68
30-49	25 774	9 712	4 735	4 575	402
≥50	14 550	6 412	3 655	2 311	446
Weighted colon radiation dose (mGy):					
<5	38 509	8 440	4 247	3 723	470
5-	23 427	5 089	2 637	2 205	247
50-	12 508	2 838	1 405	1 305	128
200-	6 356	1 485	735	680	70
500-	3 424	745	363	342	40
1000-	1 763	341	176	158	7
≥2000	624	116	59	50	7

Stroke

The excess relative risk per Gy for stroke based on the linear model over the full dose range was 9% (1% to 17%, P=0.02) (table 2). Figure 1 shows estimates of the shape of the dose-response curve for all stroke, including the fitted linear and linear-quadratic models. The test for non-linearity based on a comparison of linear and linear-quadratic dose-response models was not statistically significant (P=0.17), but the pure quadratic model, which suggests relatively little risk at lower doses, nominally provided a slightly better fit (difference in Akaike information criterion statistics of 1.87) than did the linear model. This was confirmed by analyses of lower dose ranges which showed excess relative risk per Gy of 3% (−10% to 16%) for 0-1 Gy and −7% (−28% to 16%) for 0-0.5 Gy. Figure 1 also shows no apparent risk for the lower part of the dose range; a non-negligible threshold may exist below which no excess occurs. The best estimate of a threshold dose was 0.5 Gy with an upper 95% confidence limit of about 2 Gy. However, the lower 95% confidence limit was not greater than 0, so no threshold dose may exist.

An analysis of effect modification of the risk of stroke by sex, attained age, and age at exposure showed a statistically significant difference for attained age (P=0.04): the radiation excess relative risk per Gy for stroke was higher before age 60 than after, especially among men (web table A). We also found a non-significant indication (P=0.23) that the risk of stroke associated with radiation may be highest after exposure at young ages: the excess relative risk per Gy were 36%, 9%, 15%, and 5% for ages <10, 10-19, 20-39, and ≥40. An evaluation of subtypes of stroke was not very meaningful because, before the 1990s, differential diagnosis was often not done, resulting in many cases being classified as stroke, not otherwise specified.

Heart disease

The excess relative risk per Gy for all heart disease based on the linear model in the full dose range was 14% (6% to 23%, p<0.001) (table 2). Figure 2 shows the results for the linear and linear-quadratic models. The test for non-linearity based on a comparison of linear and linear-quadratic dose-response models was not statistically significant (P>0.5). A pure linear model fitted the data nominally better than did a pure dose-squared model (difference in Akaike information criterion statistics of 2.47). The excess relative risks per Gy for heart disease over restricted dose ranges were similar to that for the full dose range. Specifically, the excess relative risk per Gy based on the linear model for the dose ranges under 2, 1, and 0.5 Gy were 14% (4% to 25%), 18% (3% to 33%), and 20% (−5% to 45%). In figure 2, the slope over the lower part of the dose range was almost identical to the one for the entire dose

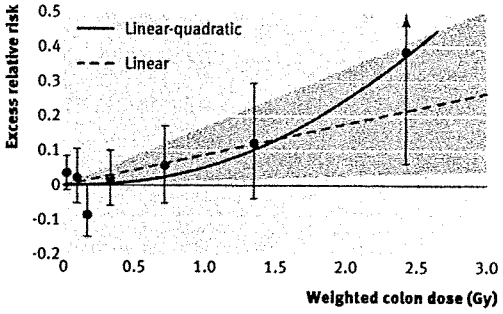

Fig 1 | Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

Table 2 | Summary excess relative risks (ERR)* per Gy and excess additive risks per 10^4 person year Gy† (EAR/10^4 PY-Gy) for types of circulatory disease mortality

Circulatory disease	Indicated as underlying cause of death				Underlying or contributing cause of death	
	Deaths	P value	% ERR/Gy (95% CI)	EAR/10^4 PY-Gy (95% CI)†	Deaths	% ERR/Gy (95% CI)
Total	19 054	<0.001	11 (5 to 17)	5.5 (2.7 to 8.4)	25 113	15 (10 to 20)
Stroke	9 622	0.02	9 (1 to 17)	2.3 (0.4 to 4.4)	12 139	12 (5 to 19)
Heart disease	8 463	<0.001	14 (6 to 23)	3.2 (1.3 to 5.2)	14 018	18 (11 to 25)
Other	969	>0.5	2 (−18 to 29)	0.1 (−0.4 to 0.7)	5 846	58 (45 to 72)

*Estimates based on linear model, adjusted for city, sex, age at exposure, and attained age.
†Average EARs calculated directly from fitted ERR models.

range. The best estimate of a threshold dose was 0 Gy, with an upper 95% confidence limit of about 0.5 Gy. We found no significant modification of effect by sex, age at exposure, or age at risk (web table A).

Analyses of different subtypes of heart disease revealed some diversity in dose-response effects (web table B) but involve a variety of uncertainties, the articulation of which is beyond the scope of this report. The risk of ischaemic heart disease increased only in the higher dose categories, and the linear increase was not significant. We found stronger associations between radiation and other heart diseases, such as hypertensive heart disease and heart failure. However, unlike the relatively high accuracy in diagnosing the general category of heart disease, substantial misclassification of subtypes of heart disease occurs (see below), which limits the meaning that can be attached to the analyses of subtypes.

Confounding factors and misdiagnosis

We examined the impact of the possible confounding factors on the radiation risk estimates among the 51 965 Life Span Study participants included in the 1978 mail survey. Table 3 shows the excess relative risks unadjusted and adjusted for six potential confounding factors. Note that the excess relative risks in table 3 differ slightly from those in table 2, because the estimates in table 3 are based on only the subcohort of the Life Span Study, whereas those in table 2 are based on the full cohort (86 611 participants). Although smoking, alcohol intake, education, type of occupation, obesity (body mass index), and diabetes were risk factors for heart disease and stroke in their own right (for example, the relative risks for heart disease were 1.4 for smoking, 1.6 for diabetes, 1.1 for body mass index 25 or over, and 0.75 for university education), they showed virtually no confounding with dose of radiation. That is, adjustment for the six variables simultaneously produced inconsequential changes in the excess relative risk per Gy: only 0.1% for heart disease and −0.9% for stroke (table 3). Analyses limited to respondents similarly showed little impact of the confounder variables (data not shown). These results suggest that in the Life Span Study, the associations of dose of radiation with mortality from stroke and heart disease is unlikely to be an artefact of confounding by major lifestyle, sociodemographic, or disease risk factors.

We also examined the diagnostic accuracy of death certificates by comparing them with autopsy reports among the 1963 cases with death certificate designated circulatory disease for whom autopsies were available from our autopsy programme between 1950 and 1985.[27] For the broad categories of stroke and heart disease, the accuracy of the diagnoses on the death certificates was fairly good. For death certificates with stroke as the underlying cause of death, 86% of autopsies listed stroke as a cause; 92% of death certificates with heart disease as the underlying cause had heart disease listed as a cause on the autopsy report. Moreover, the accuracy of diagnoses on death certificates has probably improved since 1985. However, the corresponding accuracy was rather poor for the differential diagnosis of specific subcategories of stroke or heart disease (for example, 65% for cerebral infarction, 39% for cerebral haemorrhage, 69% for ischaemic heart disease, 22% for hypertensive heart disease, and 64% for rheumatic heart disease); web table B shows risk estimates for separate subcategories.

Deaths from circulatory disease based on death certificates may include misdiagnosed deaths from cancer or cases arising from cardiotoxicity due to chemotherapy or radiotherapy for cancer. To remove the effects of misdiagnosis of cases of cancer, we estimated risks after excluding people who had previous diagnoses of cancer, on the basis of our tumour registry data. These excess relative risks were reduced by about 30% compared with estimates based on the full cohort, but still

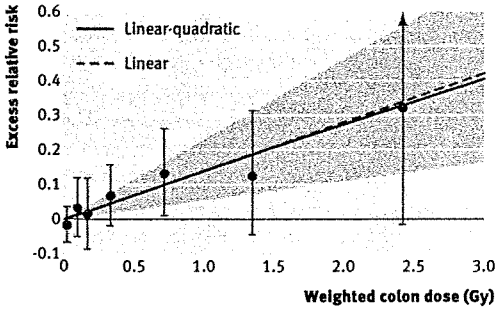

Fig 2 | Radiation dose-response relation (excess relative risk) for death from heart disease, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

Table 3 | Effects of potential confounding factors on radiation risk estimates for types of circulatory disease mortality

Circulatory disease	No of deaths	% ERR/Gy unadjusted for confounders*	% ERR/Gy adjusted for all confounders*†
Total	7907	10.0	9.6
Stroke	3366	8.1	7.2
Heart disease	4204	12.2	12.3
Other	337	2.4	0.9

ERR=excess relative risks.
*All analyses adjusted for city, sex, age at exposure, and attained age.
†Additionally adjusted for smoking, alcohol intake, education, type of household occupation, obesity (body mass index), and diabetes mellitus (on basis of about 52 000 participants).

showed a tendency to significant dose-response effects. Excluding previous cases of cancer changed the excess relative risk per Gy from 10.8% to 7.3% (dose-response P=0.008) for all circulatory disease, from 8.8% to 6.2% (P=0.11) for stroke, and from 14.0% to 9.5% (P=0.03) for heart disease.

Although we used the designated underlying cause of death in the mortality analyses, selecting a single cause of death is difficult when several correlated diseases or conditions contributed to death. Therefore, we examined the risks on the basis of both underlying and contributing causes of death (table 2). The radiation dose-response effects were nominally higher than those based on underlying cause of death alone (12% *v* 9% excess relative risk per Gy for stroke, and 18% *v* 14% for heart disease), which lends additional support to the hypothesis of radiation risk.

DISCUSSION

This study found dose-response evidence for risk of heart disease and stroke among atomic bomb survivors over the radiation dose range 0-4 Gy (mostly 0-2 Gy) based on well characterised individual doses and essentially complete ascertainment of mortality over the period of five to 58 years after exposure to radiation. This report updates earlier brief reports of a dose related excess of circulatory disease among atomic bomb survivors.[20 28 29] These results, based on about 25% more deaths than the previous paper, are substantially stronger, and we now provide more elaboration of the associations.

As shown in table 1, at the youngest ages of exposure (more recent birth cohorts) the deaths from heart disease outnumber those from stroke, whereas the opposite is true of the earlier birth cohorts; this reflects the general secular trends in the Japanese population. The table also shows that the cohort covers a wide range of doses but is weighted toward low doses, indicating that it has substantial capability to examine risks at low doses and to examine the shape of the dose-response curve. Because several plausible disease mechanisms centre around systemic effects after whole body irradiation, we used colon doses as an approximation to whole body doses for all analyses, although analyses using brain dose for stroke and lung dose for heart disease produced very similar results (data not shown).

Summary of features and coherence of radiation risk data

Although the data were statistically consistent with linearity over the full dose range in this study, considerable uncertainty exists about the shape of the dose-response curve in the low dose range. The extent of curvature seemed to be larger for stroke than for heart disease; a pure dose-squared model fitted the stroke data slightly better than did a pure linear model, whereas the linear model provided a better fit for heart disease. However, the dose-response effect was not statistically significant for either end point when we limited the calculation to the dose range 0-0.5 Gy, implying that evidence is limited on the risk below about 0.5 Gy. For stroke, the estimated threshold dose was 0.5 Gy, with an upper 95% confidence limit of about 2 Gy. For heart disease, the estimated threshold dose was 0 Gy, with an upper 95% confidence limit of about 0.5 Gy.

Additional analyses supported the association of radiation with stroke and heart disease. Adjustment of the data for other potential risk factors for circulatory disease—obesity, diabetes, smoking, alcohol consumption, education, and occupation—had almost no impact on the associations with radiation, whereas an analysis for possible misdiagnosis of cancer as circulatory disease showed a small diminution of radiation risk. Because the underlying cause of death is often uncertain, we also did analyses of stroke and heart disease indicated as either an underlying or contributing cause; these showed nominally stronger associations with radiation than did the analyses of underlying cause alone.

The findings of the epidemiological study of circulatory disease among atomic bomb survivors are confirmed and extended by our Adult Health Study, which consists of biennial clinical and laboratory examinations since 1958 of about 15% of the Life Span Study cohort members. The Adult Health Study has found dose related increases in the incidence of stroke and myocardial infarction and in the incidence or prevalence of hypertension, elevated serum cholesterol concentrations, and aortic arch calcification.[30-35] Late radiation effects have also been found for potential biomarker precursors of circulatory disease, including biomarkers for inflammation,[36-38] deficient immunological responses,[39] and alterations in immune cell repertoire.[40 41] The findings present a reasonably coherent picture of preclinical and clinical risk of circulatory disease associated with exposure to radiation. However, this needs to be complemented by a risk assessment of low doses based on mechanistic and animal models.

Strengths and limitations of study

This study has several strengths, including a large population not pre-selected for existing disease or occupational fitness, a wide but relatively low dose range (0->3 Gy) and well characterised doses, a 53 year follow-up with virtually complete mortality ascertainment, and corroborative evidence from

more detailed clinical and biomarker studies of risk of circulatory disease on a random subsample of the cohort.[30-41] In addition, we believe medical surveillance bias to be minimal, as all of the cohort is eligible for free, special medical care, and many people have little idea of the doses they received, so that the level of radiation related medical concern is not highly correlated with the actual dose received. In addition, the analyses of radiation dose with stroke and heart disease mortality showed that the association is reasonably robust with respect to confounding by lifestyle, sociodemographic, or other health factors or misdiagnosis.

The study also has several limitations and uncertainties. Ascertainment of circulatory disease from death certificates is of limited diagnostic accuracy and represents only a fraction of cases of incident disease. Analyses for confounders, although very important, are incomplete, lacking information on, for example, blood lipids, physical activity, and nutrition. Some selection effects due to dose related early mortality from the bombs may have occurred, although the impact of these is likely to be small.[42] Other limitations include unclear dose-response effects below about 0.5 Gy, inadequate information about possible biological mechanisms, and uncertainty about the generalisability of these results to Western populations because of differences in genetic factors, dietary and lifestyle risk factors, and baseline levels of risk for stroke and heart disease.[43]

Comparison with other studies

Although epidemiological and experimental data are limited, several studies suggest the possibility of effects of radiation on circulatory disease. Among medically exposed cohorts, excess heart disease mortality has been shown among patients who received radiotherapy for Hodgkin's lymphoma or breast cancer.[1-4 44] At somewhat lower doses, an increase in coronary heart disease was seen among patients who received radiotherapy for peptic ulcer.[9] An association was also seen among patients with scoliosis who received multiple fluoroscopic examinations,[45] but not among patients with tuberculosis who received multiple fluoroscopic examinations of the chest,[16] nor among patients who received radiographic treatment for benign gynaecological disease.[46 47]

Studies of cohorts with occupational or environmental exposure to radiation have not provided clear evidence for or against a radiation associated increase in mortality from circulatory disease. In a long term follow-up of early US radiologists, circulatory disease mortality was higher than for a comparison group of other medical specialists,[48] but a similar increase was not seen among early UK radiologists.[17] Increased mortality from circulatory disease was found among US radiological technologists who worked before 1950, when radiation exposures tended to be higher, but individual people's doses were not documented.[10] Significant associations with radiation for both stroke and heart disease were reported for emergency workers at Chernobyl,[12] although the study may have limitations related to sample selection and to variations in circulatory disease risk factors and medical surveillance. Among workers for British Nuclear Fuels, a significant dose-response association was found for ischaemic heart disease but not cerebrovascular disease.[13] No association was found between radiation dose and circulatory diseases among German uranium miners.[19] Preliminary results for the Mayak nuclear workers show a statistically significant dose-response association for ischaemic heart disease and stroke.[49] A new update of the UK national registry for radiation workers shows a marginally positive association of dose of radiation with heart disease, but further analyses suggest that the finding might be due to variations in smoking habits.[14] An analysis of combined cohorts of 275 000 nuclear workers from 15 countries who were exposed to low, well documented doses of external radiation did not show a significant association between dose of radiation and either stroke or heart disease.[15]

With the exception of the study of US radiological technologists, the studies were not able to adjust for potential lifestyle factors or other confounding factors, and some of the studies had no or only crude estimates of individual doses. Most of the studies of low doses had limited statistical power and some potential for bias; consequently, the potential for both false positive and false negative results may be high. The United Nations Scientific Committee on the Effects of Atomic Bomb Radiation (UNSCEAR) concluded that little evidence, other than the atomic bomb studies, exists to support an association between circulatory disease and radiation in the dose range less than 1-2 Gy.[50] A recent review article reached a similar conclusion,[51] although additional suggestively positive data have appeared since these reviews were written.[13 14 49]

Mechanisms of circulatory disease

Knowledge of the mechanisms by which radiation doses of 2 Gy or less may cause circulatory disease is limited. Evidence suggests that pro-inflammatory responses to radiation, cellular loss or functional changes in the endothelium, or microvascular damage may be early events in the cascade of pathogenic changes that lead to radiation related heart disease.[52-55] These may augment other risk factors, such as hypertension, high serum cholesterol, smoking, diabetes, and infection, to promote heart disease.[56] Associations between dose of radiation and long term levels of inflammatory markers have been documented among atomic bomb survivors,[36-38] possibly because of damage to the immune system.[39] Radiation associated microvascular damage to the renal parenchyma and vascular endothelial cells may promote hypertension and ischaemia.[50 57]

Conclusions and implications

The effect of radiation on risk of circulatory disease is potentially a very important public health concern.

WHAT IS ALREADY KNOWN ON THIS TOPIC

High doses of radiation to the heart or head and neck from radiotherapy cause a subsequent excess of deaths from heart disease or stroke

Whether radiation exposures at dose levels under 1 Gy also increase the risk of heart disease or stroke is not known

WHAT THIS STUDY ADDS

Radiation may increase the rates of stroke and heart disease at moderate dose levels (mainly 0.5-2 Gy), although the results below 0.5 Gy were not statistically significant

The association was reasonably robust with respect to confounding by lifestyle, sociodemographic, or other health factors or misdiagnosis

Given the widespread use of multiple computed tomography scans,[58,59] and other relatively high dose diagnostic medical procedures, as well as radiotherapy that exposes the heart, the implications are substantial insofar as effects occur at doses under 1 Gy. The potential magnitude of the risk is shown by the fact that in the Life Span Study cohort, who received whole body irradiation, the radiation related excess of deaths from circulatory diseases (about 210) is about a third as large as the total excess number of deaths from cancer (about 625).

This study provides the strongest evidence available to date that radiation may increase the rates of stroke and heart disease at moderate dose levels (mainly 0.5-2 Gy), but robust confirmatory evidence from other studies is needed. Although our results below 0.5 Gy are not statistically significant, the additional cases occurring with further follow-up time should provide more precise estimates of the risk at low doses.

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Ethical approval: The research was conducted under the formal approval of RERF's Human Investigation Committee.

Data sharing: Detailed tabulation of data used for the analysis and the statistical code are available from the corresponding author.

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