Original Contribution

Positive Associations Between Ionizing Radiation and Lymphoma Mortality Among Men

David B. Richardson, Hiromi Sugiyama, Steve Wing, Ritsu Sakata, Eric Grant, Yukiko Shimizu, Nobuo Nishi, Susan Geyer, Midori Soda, Akihiko Suyama, Fumiyoshi Kasagi, and Kazunori Kodama

The authors investigated the relation between ionizing radiation and lymphoma mortality in 2 cohorts: 1) 20,940 men in the Life Span Study, a study of Japanese atomic bomb survivors who were aged 15–64 years at the time of the bombings of Hiroshima and Nagasaki, and 2) 15,264 male nuclear weapons workers who were hired at the Savannah River Site in South Carolina between 1950 and 1986. Radiation dose-mortality trends were evaluated for all malignant lymphomas and for non-Hodgkin's lymphoma. Positive associations between lymphoma mortality and radiation dose under a 5-year lag assumption were observed in both cohorts (excess relative rates per sievert were 0.79 (90% confidence interval: 0.10, 1.88) and 6.99 (90% confidence interval: 0.96, 18.39), respectively). Exclusion of deaths due to Hodgkin's disease led to small changes in the estimates of association. In each cohort, evidence of a dose-response association was primarily observed more than 35 years after irradiation. These findings suggest a protracted induction and latency period for radiation-induced lymphoma mortality.

lymphoma; mortality; nuclear weapons; radiation, ionizing

Abbreviations: CI, confidence interval; ERR, excess relative rate; ICD, *International Classification of Diseases*; LRT, likelihood ratio test; LSS, Life Span Study; ND, not determined; NHL, non-Hodgkin's lymphoma; SRS, Savannah River Site.

Ionizing radiation has been considered as a cause of lymphoma by a number of investigators. In a review of this literature, Boice (1) concluded that the evidence of association between ionizing radiation and non-Hodgkin's lymphoma (NHL) is extremely weak and that there is no evidence of association between radiation and Hodgkin's disease. The United Nations Scientific Committee on the Effects of Atomic Radiation noted that studies of NHL following external exposure to ionizing radiation have yielded mixed results and concluded that overall there is little evidence of an association between NHL and external exposure to ionizing radiation (2). Ron (3) reached a similar conclusion, noting that evidence of association between radiation and NHL has been inconsistent and Hodgkin's disease has rarely been related to radiation exposure; and Melbye and Trichopoulos (4) stated that there is no evidence that ionizing radiation causes NHL. However, this conclusion is not

universally shared. Hartge et al. argued that the evidence suggests that ionizing radiation probably causes lymphoma (5) and observed that high doses of ionizing radiation appear to be associated with lymphoma risk in some studies of radiotherapy (6).

Lack of a consistent association between ionizing radiation and lymphoma could mean that there is no causal relation or that a causal relation is obscured by bias or deficiencies in exposure measurement, case classification, duration of follow-up, or some combination of these factors. Given that lymphoma is often an indolent disease, long-term studies of radiation-exposed populations may be needed to observe an effect. The development of nuclear weapons in the early 1940s led to 2 types of epidemiologic studies that can now provide evidence regarding the radiation-lymphoma association: studies based on follow-up of workers exposed to ionizing radiation during nuclear weapons

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Correspondence to Dr. David B. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 (e-mail: david.richardson@unc.edu).

production and studies based on follow-up of people exposed to ionizing radiation from the use of nuclear weapons. Most prominent among the latter is the Life Span Study (LSS), a study of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki. Radiation risk estimates from studies of nuclear workers are often compared with estimates from the LSS in order to evaluate the consistency of risk estimates in a population that includes people exposed to acute high doses with estimates from populations that are chronically exposed to low doses (7–9).

We examined the association between ionizing radiation and lymphoma mortality in a US occupational cohort and in a sample of LSS atomic bomb survivors and compared findings from the 2 populations. Follow-up of each cohort commenced in 1950 and spanned approximately 5 decades. To the extent possible, we conducted these analyses as parallel analyses employing comparable methods. We focused, in particular, on variation in the associations between radiation dose and lymphoma mortality by time since exposure.

MATERIALS AND METHODS

The LSS cohort includes 86,611 people who were alive at the time of the 1950 Japanese census, reported being in Hiroshima or Nagasaki at the time of the bombings (August 1945), and had dose estimates based on the DS02 dosimetry system (10). Follow-up for ascertainment of vital status and cause-of-death information started on October 1, 1950, and continued until December 31, 2000.

The Savannah River Site (SRS) was constructed near Aiken, South Carolina, in 1950 as a facility to produce materials for the US nuclear weapons program. A cohort of 18,883 workers who were hired at the SRS prior to 1987, who worked there for at least 90 days, who were not known to have been employed at another US Department of Energy facility, and who had complete information on name, Social Security number, sex, date of birth, and date of hire was enumerated (11). Vital status and cause-of-death information were ascertained through December 31, 2002.

Cohort restrictions for comparability

Since over 95% of the collective dose at SRS was incurred by males, there was little ability to estimate risk due to radiation exposure among female SRS workers. We therefore restricted the analyses to males in both cohorts. Since the youngest age at hire at SRS was 15 years and most SRS workers terminated their employment by age 65 years, LSS analyses were restricted to people who were aged 15–64 years at the time of the bombings. This resulted in a cohort of 15,264 male SRS workers and a cohort of 20,940 male LSS subjects who were aged 15–64 years at the time of the bombings.

Dosimetry data

For the LSS, we used DS02 revised colon dose estimates adjusted for dosimetry errors, with shielded kerma estimates above 4 Gy truncated to 4 Gy (12). For consistency with analyses of the SRS cohort, dose estimates calculated as the sum of the γ-radiation dose plus 10 times the neutron dose are expressed in sieverts; some recent reports on LSS analyses refer to this quantity as the weighted dose in grays (13, 14). Interactions between radiation and lymphocytes may occur in the lymphatic or circulatory system at a variety of anatomic sites; the choice of target organ for dose estimation may depend on the characteristics of the lymphoma, including anatomic location (15, 16). The colon dose has been taken as a representative dose to the organs involved at a variety of anatomic locations, similar to the approach employed in prior analyses of solid cancers (17). The colon dose estimate has been used by previous investigators as an estimate comparable to the quantity estimated by the radiation dosimeters worn by nuclear industry workers (i.e., the "deep dose").

For SRS workers, the exposure of interest was defined as cumulative whole-body radiation dose equivalent from external sources and tritium received during employment at the site, expressed in sieverts; neutron doses were multiplied by a factor of 10. Personal radiation monitoring data were available for the period 1950–1999. Whole-body doses were estimated for work-years with missing dose data using dose estimates from adjacent time periods and average values for similar workers; estimated annual doses constituted 4% of employment years for male workers (18).

Outcome definitions

In the LSS, underlying cause of death was coded according to the *International Classification of Diseases*, Ninth Revision (ICD-9), which was issued in 1977. In the SRS study, underlying cause of death was coded according to the Eighth Revision of the ICD (ICD-8) for deaths occurring prior to 1979 and according to the ICD revision in effect at the time of death for deaths occurring in 1979 or later. (The Tenth Revision of the ICD (ICD-10) was issued in 1992.)

As in prior analyses (17, 19), we examined the broad category of malignant lymphoma (ICD-8 and ICD-9 codes 200–202; ICD-10 codes C81–C85). In addition, we examined the subcategory of NHL (ICD-8 and ICD-9 codes 200 and 202; ICD-10 codes C82–C85). There were too few deaths due to Hodgkin's disease to support separate analyses of that outcome in these cohorts.

Statistical methods

Poisson regression methods were used. The analytical data file for the LSS cohort consisted of a tabulation of person-time and numbers of deaths by city, age at exposure (in 5-year intervals), attained age (in 5-year intervals), calendar time (1950–1952, 1953–1955, and then 5-year intervals up to 1995, 1996–1997, and 1998–2000), and dose (<0.005, 0.005–<0.02, 0.02–<0.04, 0.04–<0.06, 0.06–<0.08, 0.08–<0.1, 0.1–<0.125, 0.125–<0.150, 0.150–<0.175, 0.175–<0.2, 0.2–<0.25, 0.25–<0.3, 0.3–<0.5, 0.5–<0.75, 0.75–<1, 1–<1.25, 1.25–<1.5, 1.5–<1.75, 1.75–<2, 2–<2.5, 2.5–<3, and ≥3 Sv). The analytical data

file for the SRS cohort consisted of a tabulation of person-time and events by attained age (in 5-year intervals), race (black vs. other), year of birth (before 1915, 1915–1924, 1925–1929, 1930–1934, 1935–1949, or 1950 or later), pay code (paid monthly, weekly, or hourly), employment status (employed, terminated within the last 2 years, or terminated more than 2 years prior, classified separately for risk ages <62 years and ≥62 years) (20–22), and dose (0, >0–<0.005, 0.005–<0.02, 0.02–<0.04, 0.04–<0.06, 0.06–<0.08, 0.08–<0.1, 0.1–<0.125, 0.125–<0.150, 0.150–<0.175, 0.175–<0.2, 0.2–<0.25, 0.25–<0.3, and ≥0.3 Sv).

Covariate control was achieved through background stratification of regression models. In analyses of the LSS cohort, the stratifying factors were attained age, age at exposure, and city; in analyses of the SRS cohort, the stratifying factors were attained age, birth cohort, race, pay code, and employment status. Radiation dose-mortality associations were estimated via a regression model of the form

$$\text{rate} = e^{\alpha_i}(1 + \beta x),$$

where α_i indexes the stratum-specific mortality rate in the absence of radiation exposure and $\hat{\beta}$ provides an estimate of the excess relative rate (ERR) per sievert (23, 24).

In analyses of the LSS cohort, x represents the estimated radiation dose delivered at the time of the bombings in August 1945. Since follow-up of the LSS cohort began in October 1950, this implies a minimal lag of approximately 5 years between exposure and its effect. We also present results from analyses in which we assumed that there was no excess risk during the period 1950–1955; that is, a minimum latency period of approximately 10 years was assumed. A 10-year lag assumption has been used in previous nuclear worker studies that examined lymphoma mortality (25, 26). We refer to analyses of LSS data that examine excess mortality risk since 1950 and since 1956 as analyses carried out under 5- and 10-year lag assumptions, respectively. In analyses of the SRS cohort, x represents the cumulative radiation dose under a 5- or 10-year lag assumption. Lagging dose assignment by L years means that an increment of dose was included in the calculation of cumulative dose at time t if it had been received at or before time $t - L$ years; person-time and events at time t were then classified according to that category of lagged cumulative dose.

The dose range in the LSS, 0–4 Sv, was wider than the dose range in the SRS study (0–<0.5 Sv). In order to evaluate dose-response associations over a comparable range of doses, we also conducted analyses based upon LSS data limited to the 19,183 survivors with doses in the range of 0–<0.5 Sv.

In analyses of the LSS cohort, we assessed variation in radiation risk with time since exposure via a regression model of the form

$$\text{rate} = e^{\alpha_i}(1 + \beta_1 x\text{Period1} + \beta_2 x\text{Period2} + \beta_3 x\text{Period3} + \beta_4 x\text{Period4}),$$

where Period1–Period4 are indicator variables for the calendar time periods 1950–1970, 1971–1980, 1981–1990, and 1991–2000, respectively. The values $\hat{\beta}_1$, $\hat{\beta}_2$, $\hat{\beta}_3$, and $\hat{\beta}_4$ pro-

vide estimates of the ERR per 1-Sv dose during the periods 5–25, 26–35, 36–45, and 46–55 years after the bombings. In analyses of the SRS cohort, we fitted a model of the form

$$\text{rate} = e^{\delta_i}(1 + \phi_1 d_1 + \phi_2 d_2 + \phi_3 d_3),$$

where d_1–d_3 represent the cumulative radiation doses accrued in the exposure time windows 5–25, 26–35, and ≥36 years prior to observation of a person-year or event and $\hat{\phi}_1$, $\hat{\phi}_2$, and $\hat{\phi}_3$ provide associated estimates of the ERR per 1-Sv dose.

We estimated parameters using the EPICURE statistical package (Hirosoft International Corporation, Seattle, Washington); for consistency with recent reports (2, 26), we generated 90% confidence intervals for estimated parameters via the likelihood method (27). In some analyses, confidence bounds could not be determined (designated "not determined" (ND)). In order to aid interpretation of model fittings, we report the 1-sided P value derived via a likelihood ratio test (LRT) for each reported point estimate. Tabulations of observed versus expected numbers of deaths by category of cumulative dose are reported; we calculated expected counts for each cell of the person-time table using a regression model that included all variables except the dose term.

RESULTS

With follow-up through 2000, 90 malignant lymphoma deaths were observed among the male atomic bomb survivors exposed at ages 15–64 years, including 6 deaths from Hodgkin's disease (Table 1). Sixty-three malignant lymphoma deaths occurred among residents of Hiroshima (58 due to NHL) and 27 malignant lymphoma deaths occurred among residents of Nagasaki (26 due to NHL). No deaths due to malignant lymphoma occurred among survivors at attained ages less than 30 years. In the SRS cohort, 56 lymphoma deaths were observed; 5 of these deaths were due to Hodgkin's disease. One death due to malignant lymphoma was observed among black males (it was a case of NHL), and 18, 14, and 24 deaths due to malignant lymphoma were observed among workers paid monthly, weekly, and hourly, respectively. Three deaths due to malignant lymphoma occurred among actively employed SRS workers (all were cases of NHL) and 6 deaths occurred within 2 years of termination of employment (all were cases of NHL), while the remaining 47 deaths due to malignant lymphoma occurred 2 or more years after termination of employment at SRS (42 due to NHL).

In the LSS, the estimated ERR of malignant lymphoma per sievert, under a 5-year lag assumption, was 0.79 (90% confidence interval (CI): 0.10, 1.88). The goodness of model fit was slightly improved, and the magnitude of association was slightly increased, upon exclusion of deaths due to Hodgkin's disease (Table 2). Under a 10-year lag assumption, these estimated associations were slightly larger in magnitude. In the SRS study, the estimated ERRs of malignant lymphoma per sievert under 5- and 10-year lag assumptions were 6.99 (90% CI: 0.96, 18.39) and 8.18 (90% CI: 1.44, 21.16), respectively. Upon exclusion of deaths due to

Table 1. Observed Numbers of Deaths Due to Malignant Lymphoma Among Male Atomic Bomb Survivors (1950–2000) and Male Workers at the Savannah River Site (1950–2002), by Age Group, Japan and South Carolina[a]

Attained Age, years	Atomic Bomb Survivors[b]			Savannah River Site Workers		
	Person-Years of Follow-Up	No. of Deaths		Person-Years of Follow-Up	No. of Deaths	
		Malignant Lymphoma	Non-Hodgkin's Lymphoma		Malignant Lymphoma	Non-Hodgkin's Lymphoma
<35	50,103	1	1	119,174	2	2
35–39	31,253	2	1	66,573	2	2
40–44	39,991	3	2	66,937	2	2
45–49	50,727	3	3	61,141	0	0
50–54	63,495	6	4	53,782	3	3
55–59	73,109	4	4	47,115	4	4
60–64	76,830	9	9	41,019	4	3
65–69	74,314	14	13	33,865	15	11
70–74	58,446	19	19	21,880	15	15
75–79	37,956	17	16	9,712	5	5
≥80	35,138	12	12	4,494	4	4
Total	591,359	90	84	525,691	56	51

[a] Because of rounding, column totals for person-time differ slightly from the sums of rows.
[b] Japanese males who were aged 15–64 years and present in Hiroshima or Nagasaki at the time of the bombings.

Hodgkin's disease, these estimated associations were slightly smaller in magnitude. The SRS cohort included a single death due to malignant lymphoma among black workers; upon restriction to nonblack workers, the estimated ERRs of malignant lymphoma per sievert under 5- and 10-year lag assumptions were 7.10 (90% CI: 1.00, 18.66) and 8.18 (90% CI: 1.44, 21.16), respectively.

When the LSS data were limited to survivors with doses in the range of 0–<0.5 Sv, estimates of radiation-lymphoma mortality associations were of greater magnitude than estimates obtained from model fittings over the entire dose range. Under a 5-year lag assumption, the estimated ERRs of malignant lymphoma and NHL per sievert were 3.02 (90% CI: 0.33, 7.22) and 2.86 (90% CI: 0.10, 7.24), respectively. While this suggests nonlinearity in the dose-response association, comparison of a linear-quadratic dose-response function with a purely linear dose-response function indicated that inclusion of a quadratic term resulted in very little improvement in model fit (LRT = 0.07, 1 df; P = 0.79). Under a 10-year lag assumption, the estimated ERRs of malignant lymphoma and NHL per sievert were 4.54 (90% CI: 1.16, 9.93) and 4.24 (90% CI: 0.83, 9.76), respectively.

In the LSS, there was no evidence of an association between radiation dose and lymphoma mortality during the periods 5–25 years or 26–35 years after irradiation (Table 3). Positive associations between lymphoma mortality and dose were observed during the periods 36–45 years and 46–55 years after irradiation. Analyses of associations between radiation dose and NHL led to risk estimates similar to those obtained via analyses of all malignant lymphoma (Table 3). In a nested model, defined post hoc, we evaluated the asso-

ciation between dose and malignant lymphoma mortality during the periods 5–35 years postexposure and 36–55 years postexposure. There was no evidence of association 5–35 years after exposure (ERR/Sv = 0.03, 90% CI: ND, 1.15; LRT = 0.00, P = 0.96); however, there was a positive

Table 2. Estimated Association Between Lymphoma Mortality and Ionizing Radiation Dose Under 5- and 10-Year Exposure Lags Among Male Atomic Bomb Survivors (1950–2000) and Male Workers at the Savannah River Site (1950–2002), Japan and South Carolina

Exposure Lag and ERR	Atomic Bomb Survivors[a]		Savannah River Site Workers	
	Malignant Lymphoma	Non-Hodgkin's Lymphoma	Malignant Lymphoma	Non-Hodgkin's Lymphoma
5 years				
ERR per Sv	0.79	0.86	6.99	6.45
90% CI	0.10, 1.88	0.13, 2.03	0.96, 18.39	0.48, 17.95
P value[b]	0.05	0.04	0.04	0.07
10 years				
ERR per Sv	1.06	1.12	8.18	7.62
90% CI	0.24, 2.38	0.26, 2.51	1.44, 21.16	0.93, 20.77
P value	0.02	0.02	0.03	0.05

Abbreviations: CI, confidence interval; ERR, excess relative rate.
[a] Japanese males who were aged 15–64 years and present in Hiroshima or Nagasaki at the time of the bombings.
[b] P value from a likelihood ratio test that the reported parameter for the estimated ERR was equal to 0.

Table 3. Estimated Association Between Radiation Dose and Lymphoma Mortality Among Male Atomic Bomb Survivors,[a] by Time Since Exposure, Hiroshima and Nagasaki, Japan, 1950–2000

Lymphoma Type and ERR	Time Since Exposure, years (Calendar Period)			
	5–25 (1950–1970)	26–35 (1971–1980)	36–45 (1981–1990)	46–55 (1991–2000)
Malignant lymphoma				
ERR per Sv	0.08	−0.10	2.23	1.70
90% CI	ND, ND	ND, ND	0.09, 6.91	0.16, 5.36
P value[b]	0.89	0.91	0.08	0.05
No. of deaths	31	20	16	23
Non-Hodgkin's lymphoma				
ERR per Sv	0.17	−0.10	2.23	1.70
90% CI	ND, ND	ND, ND	0.09, 6.91	0.16, 5.36
P value	0.79	0.91	0.08	0.05
No. of deaths	25	20	16	23

Abbreviations: CI, confidence interval; ERR, excess relative rate; ND, not determined.

[a] Japanese males who were aged 15–64 years and present in Hiroshima or Nagasaki at the time of the bombings.

[b] P value from a likelihood ratio test that the reported parameter for the estimated ERR was equal to 0.

association between dose and lymphoma mortality ≥36 years after exposure (ERR/Sv = 1.93, 90% CI: 0.48, 4.66; LRT = 6.83, $P < 0.01$).

In analyses of the SRS cohort, there was a highly imprecise positive association between lymphoma mortality and doses accrued during the periods 5–25 and 26–35 years prior. The association with doses accrued ≥36 years prior was of the largest magnitude and contributed most to the goodness of model fit. The estimated dose-response association within each exposure time window was based on the total number of lymphoma deaths. Similar estimates were obtained in analyses restricted to NHL (Table 4).

When the LSS data were limited to those survivors with doses in the range of 0–<0.5 Sv, there were positive, albeit imprecise, estimates of association between radiation dose and malignant lymphoma mortality during the periods 5–25 years after irradiation (ERR/Sv = 0.64, 90% CI: −1.69, 5.94; LRT = 0.1, $P = 0.75$), 26–35 years after irradiation (ERR/Sv = 2.52, 90% CI: −1.48, 11.71; LRT = 0.7, $P = 0.40$), 36–45 years (ERR/Sv = 7.08, 90% CI: −0.08, 22.86; LRT = 2.6, $P = 0.11$), and 46–55 years after irradiation (ERR/Sv = 6.42, 90% CI: −0.22, 23.11; LRT = 2.4, $P = 0.12$). Results for analyses of NHL were similar to those for all lymphoma mortality. There was a negative association between radiation dose and NHL mortality during the period 5–25 years after irradiation (ERR/Sv = −0.41, 90% CI: ND, 5.00; LRT = 0.03, $P = 0.85$) and positive associations between radiation dose and mortality during the periods 26–35 years after irradiation (ERR/Sv = 2.46, 90% CI: −1.50, 11.55; LRT = 0.68, $P = 0.41$), 36–45 years after irradiation (ERR/Sv = 7.07, 90% CI: −0.08, 22.83; LRT = 2.61, $P = 0.11$), and 46–55 years after irradiation (ERR/Sv = 6.42, 90% CI: −0.23, 23.11; LRT = 2.41, $P = 0.12$).

Table 5 shows observed and expected numbers of malignant lymphoma deaths by dose category under 5- and 10-year lag assumptions. The distribution of events among SRS workers with respect to dose was relatively narrow in comparison with the LSS data. Over the dose range at which the ratio of observed to expected numbers of malignant lymphoma deaths could be compared in these 2 cohorts (i.e., 0–<0.5 Sv), these ratios were similar in magnitude for analyses of the 2 cohorts, although values tended to be slightly greater for the SRS cohort than for the LSS cohort. Ratios of observed to expected numbers of deaths were

Table 4. Estimated Association Between Radiation Dose and Lymphoma Mortality Among Male Workers at the Savannah River Site, by Time Since Exposure, South Carolina, 1950–2002

Lymphoma Type and ERR	Time Since Exposure, years		
	5–25	26–35	36–52
Malignant lymphoma			
ERR per Sv	1.18	4.06	33.28
90% CI	ND, ND	ND, 25.34	4.83, 107.9
P value[a]	0.85	0.64	0.03
Non-Hodgkin's lymphoma			
ERR per Sv	1.51	0.58	38.35
90% CI	ND, 16.02	ND, 22.83	7.02, 121.57
P value	0.80	0.95	0.02

Abbreviations: CI, confidence interval; ERR, excess relative rate; ND, not determined.

[a] P value from a likelihood ratio test that the reported parameter for the estimated ERR was equal to 0.

Table 5. Observed and Expected Numbers of Deaths Due to Malignant Lymphoma Among Male Atomic Bomb Survivors (1950–2000) and Male Workers at the Savannah River Site (1950–2002), by Radiation Dose, Japan and South Carolina[a]

Assumed Lag and Cohort	Radiation Dose, Sv						
	<0.005	0.005–<0.10	0.10–<0.20	0.20–<0.50	0.50–<1	1–<2	≥2
5-year lag							
Atomic bomb survivors[b]							
No. of deaths observed	32	29	8	11	3	5	2
Obs/Exp ratio[c]	0.80	0.97	1.33	1.61	0.72	2.04	2.60
Mean dose, Sv	0.001	0.032	0.141	0.322	0.721	1.340	2.392
Person-years of follow-up	260,641	195,354	38,255	45,932	28,566	16,674	5,937
Savannah River Site workers							
No. of deaths observed	20	24	7	5	0	0	0
Obs/Exp ratio	0.77	1.01	1.78	2.14			
Mean dose, Sv	0.001	0.028	0.142	0.266			
Person-years of follow-up	305,131	181,767	25,961	12,830	0	0	0
10-year lag							
Atomic bomb survivors							
No. of deaths observed	27	27	8	11	3	5	2
Obs/Exp ratio	0.73	0.97	1.44	1.73	0.78	2.19	2.73
Mean dose, Sv	0.001	0.032	0.141	0.322	0.722	1.338	2.392
Person-years of follow-up	213,808	160,274	31,330	37,840	23,545	13,827	4,926
Savannah River Site workers							
No. of deaths observed	21	24	6	5	0	0	0
Obs/Exp ratio	0.77	1.05	1.60	2.35			
Mean dose, Sv	0.001	0.028	0.141	0.264			
Person-years of follow-up	344,948	149,706	21,197	9,840	0	0	0

Abbreviations: Exp, expected; Obs, observed.
[a] Because of rounding, some column totals for person-time differ slightly from the sums of rows.
[b] Japanese males who were aged 15–64 years and present in Hiroshima or Nagasaki at the time of the bombings.
[c] Ratio of the number of deaths observed to the number of deaths expected.

minimally affected by exclusion of deaths due to Hodgkin's disease (results not shown).

DISCUSSION

In a previous analysis of lymphoma mortality among survivors in the LSS, Pierce et al. (17) reported evidence of a nonsignificant positive association with radiation dose among males (ERR/Sv = 0.27, 90% CI: ND, 1.49) and a nonsignificant negative association among females (ERR/Sv = −0.17, 90% CI: ND, 0.30). In those analyses, a time-constant ERR model was fitted to mortality follow-up through 1990. In the present paper, time-window analyses helped to explain the observation of a significant positive association between radiation dose and lymphoma mortality among male atomic bomb survivors with more recent follow-up, showing that positive associations have been observed only since 1980. Such findings suggest a protracted induction and latency period. If considered within the framework of a multistage model of carcinogenesis, the relatively long empirical induction period for lymphoma

following radiation exposure may be consistent with action at an early stage of a multistage process.

The point estimates for the radiation dose-lymphoma mortality association under 5- and 10-year lag assumptions derived from analysis of the SRS cohort are larger than the estimates derived from analysis of the LSS cohort (Table 2). Differences in the magnitude and rate of exposure may influence the comparability of dose-response estimates. These cohorts also differ with regard to potential biases from confounding, selection, and exposure measurement error. While it is not an established cause of NHL, benzene is suspected to be related to NHL (28). However, benzene was not used in the production process at SRS, nor was it routinely used as a degreaser. Plutonium-239 is a radiologic hazard at SRS. While a recent study suggested that the contribution of plutonium doses to total dose estimates for these workers was relatively small (29), we did not directly assess confounding by plutonium exposure. Selection bias could have influenced these estimates of association—for example, via the "healthy worker" survivor effect (20). Although we adjusted for employment status, such an approach is suboptimal if employment status is an intermediate variable

as well as a confounder of the association of interest. However, in studies of chronic diseases with long latency periods, cumulative exposure will typically not appreciably influence employment termination rates; under such conditions, employment status will play a minor role as an intermediate variable but could have a strong role as a confounder of the association (22). Frequent reading of dosimeters could have led to dose underestimation if dosimeters were not sufficiently exposed to reach a minimum detectable dose. However, prior work suggests that the impact of this source of measurement error on estimates of radiation dose-response trends is modest (30–32).

Problems of bias could also influence estimates of radiation-mortality associations among atomic bomb survivors. DS02 estimates account for the initial radiation released from the detonation of the weapons but not radiation from fallout or neutron activation of the ground and structures (33). The available data suggest that most people in Hiroshima and Nagasaki had low cumulative external doses from fallout, with maximum estimates in the range of 0.2–0.4 Sv for several hundred people who were in an area of Nagasaki approximately 3 km from the hypocenter (33, 34). Selective survival in the LSS cohort is another concern and is a generic consideration when trying to understand the temporal evolution of exposure-related risk (35). A relation between short-term survival after the bombings and later risk of lymphoma could lead to bias in dose-response estimates. Evidence of selection has been suggested by some empirical analyses (36, 37); however, values for the magnitude of dose-related selective survival assumed in a recent study suggested a modest potential for bias in dose-response estimates (38).

These analyses provide evidence of a positive association between ionizing radiation dose and malignant lymphoma mortality among male Japanese atomic bomb survivors and SRS workers. We did not address risk estimates for females, for whom there was no evidence of a positive association between radiation dose and lymphoma mortality in follow-up through 1990 (17). The radiation-NHL mortality associations among these male atomic bomb survivors and SRS workers are of larger magnitude than the estimate reported in a 15-country study of nuclear workers (under a 10-year lag assumption, ERR/Sv = 0.44, 90% CI: <0, 4.78) (7); however, in the current analyses, positive dose-response associations were primarily observed more than 35 years after irradiation. These findings underscore the importance of continued follow-up of the LSS cohort and nuclear worker cohorts.

ACKNOWLEDGMENTS

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