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The Incidence of Leukemia, Lymphoma and Multiple Myeloma among Atomic Bomb Survivors: 1950–2001

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A marked increase in leukemia risks was the first and most striking late effect of radiation exposure seen among the Hiroshima and Nagasaki atomic bomb survivors. This article presents analyses of radiation effects on leukemia, lymphoma and multiple myeloma incidence in the Life Span Study cohort of atomic bomb survivors updated 14 years since the last comprehensive report on these malignancies. These analyses make use of tumor- and leukemia-registry based incidence data on 113,011 cohort members with 3.6 million person-years of follow-up from late 1950 through the end of 2001. In addition to a detailed analysis of the excess risk for all leukemias other than chronic lymphocytic leukemia or adult T-cell leukemia (neither of which appear to be radiation-related), we present results for the major hematopoietic malignancy types: acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, adult T-cell leukemia, Hodgkin and non-Hodgkin lymphoma and multiple myeloma. Poisson regression methods were used to characterize the shape of the radiation dose-response relationship and, to the extent the data allowed, to investigate variation in the excess risks with gender, attained age, exposure age and time since exposure. In contrast to the previous report that focused on describing excess absolute rates, we considered both excess absolute rate (EAR) and excess relative risk (ERR) models and found that ERR models can often provide equivalent and sometimes more parsimonious descriptions of the excess risk than EAR models. The leukemia results indicated that there was a nonlinear dose response for leukemias other than chronic lymphocytic leukemia or adult T-cell leukemia, which varied markedly with time and age at exposure, with much of the evidence for this nonlinearity arising from the acute myeloid leukemia risks. Although the leukemia excess risks generally declined with attained age or time since exposure, there was evidence that the radiation-associated excess leukemia risks, especially for acute myeloid leukemia, had persisted throughout the follow-up period out to 55 years after the bombings. As in earlier analyses, there was a weak suggestion of a radiation dose response for non-Hodgkin lymphoma among men, with no indication of such an effect among women. There was no evidence of radiation-associated excess risks for either Hodgkin lymphoma or multiple myeloma.

INTRODUCTION

A radiation-related excess of leukemia in radiologists and physicians was recognized in the early 1940s (*1*, *2*). By the late 1940s, physicians in Hiroshima and Nagasaki had noticed an apparent increase in leukemia incidence among survivors (particularly children) who were near the hypocenters at the time of the atomic bombs. The first published report of an increased risk of leukemia among the atomic bomb survivors appeared in 1952 (*3*). Since then, risks of leukemia and other hematological malignancies have been the subject of special and continuing interest in studies of the survivors conducted at the Radiation Effects Research Foundation (RERF), formerly the Atomic Bomb Casualty Commission (ABCC).

The latest comprehensive analysis of the incidence of hematological malignancies in the RERF Life Span Study (LSS) cohort of the atomic bomb survivors (*4*) considered radiation effects on all leukemias as a group and on selected leukemia subtypes for the period from 1950–1987. Radiation effects on leukemia mortality have been considered in most of the periodic LSS mortality reports and

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reports on dosimetry changes and temporal patterns of risk (*5–7*).

Incident cases used in the analyses presented here were identified by the Leukemia and Tumor/Tissue Registries in Hiroshima and Nagasaki with follow-up through the end of 2001, fifty-five years after the bombings and 14 years beyond that used in the previous comprehensive report. Analyses are presented for all leukemias other than chronic lymphocytic leukemia (CLL) or adult T-cell leukemia (ATL) as a group (leukemia other than CLL or ATL) as well as for major leukemia subtypes [acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML)] and CLL, ATL, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and multiple myeloma (MM). In the leukemia analyses herein, we focus on how the excess risk varies with gender, age at exposure and attained age or time since exposure, as well as the characterization of curvature in the leukemia dose response. In contrast to the previous incidence analyses that focused solely on excess absolute rates (*4*), the present analyses focused on both excess relative risks and excess rates. A question of particular interest with regard to leukemia was whether or not there were any indications of a radiation-associated increase in risks 30 or more years after exposure. For lymphomas and MM, where the excess risks, if any, appear to be considerably lower than those for leukemia, our analyses primarily focused on the evidence for a statistically significant dose response.

MATERIAL AND METHODS

Study Population and Cohort Follow-up

In the late 1950s, records from the 1950 special national census of atomic bomb survivors were used by ABCC researchers to establish a fixed cohort of atomic bomb survivors: the LSS cohort. The LSS cohort includes 93,741 survivors who were residents of Hiroshima and Nagasaki, were present within 10 km of the hypocenters at the time of the bombs and were alive on October 1, 1950, and 26,580 Hiroshima and Nagasaki residents who were not in the cities at the time of the bombings. The latter group, which is referred to as the not-in-city (NIC) group, is similar in size and frequency-matched on gender and age at the time of the bombings to survivors in the cohort who were within 2.5 km of the hypocenters. The present analyses were based on the 113,011 cohort members for whom dose estimates are available. Dose estimates are not available for 7,044 cohort members because of uncertain locations or shielding configurations. Almost 60% of the cohort members are women and 41% were less than 20 years old at the time of the bombings. As of the end of follow-up for the present analyses (December 31, 2001), 43% of the cohort members were still alive. Additional information on the characteristics and history of the LSS cohort can be found in previously published articles (*4–6*, *8*).

Until recently, it has been customary to exclude the NIC group from risk analyses because concerns about possible differences in socioeconomic status or other factors that might affect risk estimates. However, as in the most recent LSS solid cancer incidence analyses (*9*), the NIC group was used in this work to augment the information on variation in baseline rates by gender, attained age and birth cohort, but not on the overall level of the rates. This was accomplished by the inclusion of fitted increments associated with a city-specific NIC indicator in the baseline risk model.

Vital status for individual LSS cohort members is ascertained by linkage to the national family registration (*koseki*) system on a 3-year cycle. Given the comprehensive nature of the *koseki* system, only 175 (<1%) cohort members have been lost to follow-up. Information from *koseki* records is used to trace death certificates, which provide information on causes of death for those known to have died. Incidence follow-up began on October 1, 1950. The end of follow-up is the earliest date of diagnosis of the first primary malignancy (of any type), the date of death, the date of loss to follow-up or December 31, 2001.

Ascertainment of Hematological Malignancies

Leukemia registry. Two to three years after the atomic bombings of Hiroshima and Nagasaki, a number of physicians in Hiroshima and Nagasaki noted a markedly increased rate of leukemia in children living near the hypocenters (*3*). Therefore, in the early 1950s, ABCC researchers together with hematologists in Hiroshima and Nagasaki launched the Leukemia Registry program to ascertain all potential cases of leukemia and other hematological malignancies in the two areas, including cases that occurred in the late 1940s. The Leukemia Registry remained active until the late 1980s when it was supplanted by the city and prefecture cancer registries. Leukemia Registry data were the basis for a number of reports on radiation-related risk of leukemia and related diseases in the survivors (*10–15*).

The Leukemia Registry also gathered blood smears or other biological specimens used for diagnosis, clinical information, laboratory records and other material relevant to the diagnosis. These materials and information stored at ABCC and later at RERF were reviewed by at least two Leukemia Registry hematologists to develop a consensus diagnosis. Additional information on the Leukemia Registry procedures is available elsewhere (*4*, *16*). Accepted cases were assigned a diagnosis date and the type of malignancy was coded. In the mid-1980s, the materials collected by the Leukemia Registry were re-reviewed and 60% of the leukemia diagnoses were classified using the French-American-British (FAB) classification system (*17–20*).

Tumor registries. As the Leukemia Registry activities declined in the mid-1980s, the population-based Tumor Registries, independent of the Leukemia Registry, became the primary source for ascertaining leukemias and other hematological malignancies in Hiroshima and Nagasaki. The Tumor Registries were established in 1957 in Hiroshima and 1958 in Nagasaki (*21*). The Hiroshima and Nagasaki Tumor Registries are operated by RERF entrusted by Hiroshima and Nagasaki prefectures and cities. Active ascertainment from hospital records in the two cities and their outlying areas is the primary method of case identification employed by the registries. Furthermore, this is supplemented by linkage to the cause of death information and to records from the ABCC surgical pathology program, which was superseded in the early 1970s by the regional tissue registries. Records are reviewed by RERF personnel trained in nosology and coded using the International Classification of Diseases for Oncology (ICD-O) codes that were current at the time of coding (*22*).

Assembling the present case series. Incident cases considered for these analyses were ascertained and assembled from the Leukemia Registry and the Hiroshima and Nagasaki Tumor Registries using a series of rules to give precedence to the better information when there were discrepancies. Since the Leukemia Registry involved detailed hematology review, precedence was given to the Leukemia Registry diagnosis if it was at least as detailed as the Tumor Registry diagnosis. Additional review was carried out for a small number of cases in which the Leukemia Registry and Tumor Registry diagnoses appeared to be inconsistent. More detailed information can be found in (*4*).

Classification of hematologic malignancies has been modified and refined over time, particularly for myeloid leukemias. Since most of the cases in these analyses cannot be classified according to the more detailed modern classifications and the number of cases of specific

subtypes tends to be small, we used a broad classification of types for these analyses that parallels the classification used in earlier reports on risks for these cancers in the LSS. In particular, cases identified as aleukemic/subleukemic myeloid leukemias and myeloid leukemia not otherwise specified are included in the AML group. The aleukemic/subleukemic lymphoid leukemias are combined with ALL. The CLL group includes CLL and hairy cell leukemia. ICD-O morphology codes included in the various analysis groups are given in supplementary Table S1 (http://dx.doi.org/10.1667/RR2892.1.S1)

Organization of the data for analysis. The primary Poisson regression analyses for this report were based on a highly stratified tabulation of person-years and case counts. The stratifying factors were: city, gender, age at exposure (5-year categories to age 69 and 70 and over), attained age (5-year categories from age 5–84 and 85 and over), calendar time period (from October 1, 1950, with subsequent cut points on January 1 of 1953, 1956 and 1958, and every 5 years from 1961–2001 except for an additional cut-point at 1988 to facilitate comparison with the previous report), exposure status (<3 km from the hypocenter, 3–10 km from the hypocenter and not in a city), adjusted and truncated weighted (gamma plus 10 times the neutron) bone marrow dose (22 dose categories for survivors), and whether or not an individual's shielded kerma estimate was greater than 4 Gy based on the latest dosimetry system (DS02). The lowest dose category included people whose DS02 weighted bone marrow dose estimates were less than 5 mGy. The lower dose bounds (in Gy) for the subsequent categories were: 0.005, 0.02, 0.04, 0.06, 0.08, 0.10, 0.125, 0.150, 0.175, 0.20, 0.25, 0.30, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, and 3.0. As in other LSS incidence reports (*4*, *9*), person-years were adjusted by birth cohort, time period, gender and city-specific residence probabilities to correct for migration from the Tumor Registries' catchment areas (*23*). A table with information on the proportion of person-years lost due to migration is given in supplementary Table S3 (http://dx.doi.org/10.1667/RR2892.1.S2). The data for each stratum included migration-adjusted person-years, counts of the number of eligible cases by outcome type, and person-year-weighted mean values of weighted bone marrow dose, attained age, age at exposure and time since exposure.

Risk Models and Statistical Methods

The previous analyses (*4*) focused on age at exposure dependent excess absolute rate (EAR) models in which the radiation dose effect could vary with time since exposure within age at exposure groups. As we examined the current data, it became apparent that simpler models similar to those used for solid cancers (*9*), in which the excess risk varies smoothly with age at exposure and time can often describe the data at least as well as the models used in the previous analyses. Therefore, we considered both EAR and excess relative risk (ERR) models in which the excess risk varies with age at exposure and either attained age or time since exposure. In an EAR model, the disease rate can be written as:

$$\lambda_0(c,s,a,b) + \rho(d)\varepsilon_a(c,s,a,b).$$

While in the ERR model it is

$$\lambda_0(c,s,a,b)[1 + \rho(d)\varepsilon_r(c,s,t,e)].$$

The term $\lambda_0(c,s,a,b)$ is a parametric model for the baseline (zero dose) rates that depends on attained age (a), gender (s), and factors such as birth cohort (b) and city (c). In the primary dose-response model, $\rho(d)\varepsilon(c,s,t,e)$, $\rho(d)$ describes the shape of the dose response and $\varepsilon(c,s,t,e)$ describes effect modification associated with the effect of dose d, i.e., how the level of the radiation-related excess risk varies with city (c), gender (s), age at exposure (e) and time (t), where time can be functions of either time since exposure or attained age. For this report (as in most analyses of the LSS data) effect modification was described using log-linear functions of the variables of interest. In descriptions of these models, unless explicitly noted, they are based on log attained age and log time since exposure. In general, age at exposure and time since exposure were centered or scaled so that the dose-effect parameters correspond to the risk for a person who was 30 years old at the time of the bombings for incidence 25 (attained age 55) or 40 (attained age 70) years after exposure. For some outcomes, we considered extensions of the effect modification model, including gender-dependent age at exposure and time effects, interactions between age at exposure and time, or categorical age at exposure and time effects.

The dose response functions considered in this report included:

(a) linear $\rho(d) = \beta_1 d;$

(b) linear − quadratic $\rho(d) = \beta_1 d + \beta_2 d^2;$

(c) pure − quadratic $\rho(d) = \beta_2 d^2;$

(d) single knot linear spline/threshold models

$$\rho(d) = \theta_1 d + \theta_2 (d - c)(d > c);$$

(e) nonparametric $\rho(d) = \theta_{dcat}.$

β_1 and β_2 are the linear and quadratic dose-response parameters, respectively. In a linear-quadratic model, the curvature of the dose response is defined as the ratio of the quadratic and linear dose effects: i.e., β_2/β_1. In the single-knot linear-spline/threshold models, c is a dose join point and when θ_1 equals 0 this is a threshold model. In the nonparametric dose-response model the dose response varies by dose category without any smoothing ($\rho(d) = \theta_{dcat}$). Although the bone marrow dose estimates used in all of these analyses were adjusted to allow for the effects of dose uncertainty (*24*), dose-response models also included a multiplicative dichotomous factor for those with shielded kerma estimates in excess of 4 Gy to allow for dose uncertainties not captured by the standard adjustment methods or for high-dose effects such as cell killing.

Analyses were limited to first primary malignancies diagnosed during the follow-up period among cohort members with DS02 dose estimates. Cases that were diagnosed outside of Hiroshima or Nagasaki prefectures were excluded. Maximum likelihood estimates of the parameters in these models were computed using the data in the person-year (PY) table described above. *P* values and confidence intervals (CI) for model parameters were based on the profile likelihood function. Uncertainty in the various risk estimates were summarized using 95% confidence intervals. The models were fit using the Epicure risk regression software (*25*). Akaike information criteria (AIC) (*26*) values were used to aid in the comparison of nonnested models. The models used are described and estimates of some of the key parameters are given in the Results section. However, details of the parameterizations used and the parameter estimates for our preferred models are presented in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

RESULTS

A total of 1,215 hematological malignancies were identified among 113,011 LSS cohort members and 944 of these cases were eligible for inclusion in the analyses between 1950 and the end of 2001. Almost 40% of the eligible hematopoietic malignancies were diagnosed after the end of the follow-up (1987) used in the last comprehensive analyses of the LSS data (*4*). Table 1 provides a summary of the numbers of cases eligible for

TABLE 1
Eligible and Ineligible Cases by Exclusion Reason

Malignancy	Eligible	Ineligible				Total
		Not first primary	Nonresident[†]	Unknown dose	Before 10/1/1950	
Leukemia						
Leukemia other than CLL or ATL	312	28	31	36	9	416
Acute myeloid (AML)[‡]	176	20	13	18	2	229
Chronic myeloid (CML)	75	3	5	11	5	99
Acute lymphoblastic (ALL)[§]	43	4	9	4	2	62
Other	18	1	4	3	0	26
Chronic lymphocytic (CLL)[††]	12	4	0	0	0	16
Adult T-cell (ATL)	47	3	7	2	0	59
Any leukemia	371	35	38	38	9	491
Lymphoma and Myeloma						
Non-Hodgkin lymphoma (NHL)	402	34	33	27	5	501
Hodgkin lymphoma (HL)	35	1	4	1	1	42
Multiple myeloma (MM)	136	26	10	9	0	181
Total	944	96	85	75	15	1,215

[†] Residing outside of Hiroshima or Nagasaki prefectures at the time of diagnosis.
[‡] Includes acute myeloid leukemia (146 eligible cases) as well as acute monocytic leukemia (10 eligible cases), a-/sub-leukemic myeloid leukemia (16 eligible cases) and myeloid leukemia NOS (4 eligible cases).
[§] Includes 41 cases classified as acute lymphoblastic leukemia (41 cases) and 2 cases classified as aleukemia/subleukemic lymphoid leukemia.
[††] Includes 10 cases classified as chronic lymphocytic leukemia and 2 as hairy cell leukemia.

dose-response analyses by type of malignancy together with information on the reasons why cases were deemed ineligible. About 40% of the cases were leukemias, another 40% were identified as NHL and almost 15% were MM. Hodgkin lymphoma was uncommon. Almost half of the leukemia cases were classified as AML, 20% were CML and about 12% were ALL. All but five of 47 ATL cases were diagnosed in Nagasaki and constitute almost 40% of all of the Nagasaki leukemia cases. As with other populations in Japan, the incidence of CLL is remarkably low. All except 3 of 18 cases in the *other leukemia* group were diagnosed in Hiroshima. Eleven of the cases in this group were classified as acute leukemia not otherwise specified (NOS) and other specific types of leukemia while 7 were classified as aleukemia, subleukemia or leukemia NOS. The cases in this group were included in the leukemia other than the CLL or ATL analyses discussed below but were not analyzed separately. The crude rates for leukemia, lymphoma and multiple myeloma by age at exposure, period and dose category are given in supplementary Tables S4 and S5 (http://dx.doi.org/10.1667/RR2892.1.S2).

Leukemia Other Than CLL or ATL

While a few studies suggest that CLL risk may be affected by radiation exposure (*27–30*), a number of others do not (*31*, *32*). It is generally believed that radiation has little effect on CLL rates and it is common practice in studies of radiation effects to focus on the risk of leukemia other than CLL. In view of the unusual nature of ATL incidence, we also excluded ATL from the pooled leukemia analyses. A total of 312 cases of leukemia other than CLL or ATL were used in these analyses (Table 1).

Baseline rates for this outcome were described reasonably well by a model in which the rates increased in proportion to age. This simple pattern was significantly improved ($P < 0.001$) by allowing the power to increase with increasing attained age (i.e., by adding a quadratic term in log attained age). The nature of the increase with attained age did not differ significantly by gender ($P > 0.5$), nor did it appear to vary significantly with birth cohort ($P = 0.30$). However, at any given age the risk for women was about half that for men (female:male ratio 0.50 95% CI 0.40–0.63). Baseline rates in Nagasaki were 35% lower than in Hiroshima ($P = 0.004$). There was a significant ($P < 0.001$) nonlinear birth cohort effect with the highest age-specific rates for those born around 1920, which decreased by about 30% for people born 20 years earlier or later than this—a pattern similar to that seen in the Japanese national leukemia mortality rates (*33*). The fitted age-specific baseline rate estimates for three birth cohorts are shown in Fig. 1a. The baseline rate model and parameter estimates for leukemias other than CLL or ATL are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

Dose response and effect modification. Using a simple time-constant linear ERR model with no effect modification, there was a statistically significant ($P < 0.001$) dose-response relationship. Allowing for attained age and time since exposure effects (discussed below), a concave upward linear-quadratic (LQ) model described the data significantly better than either a linear dose response ($P = 0.001$) or pure-quadratic ($P = 0.04$) dose-response model. The estimated linear dose effect in the LQ ERR model at attained age 70 after exposure at age 30 was 0.79 per Gy and the estimated curvature was 1.20, as given in Table 3. Figure 1b illustrates the fitted dose response together with dose-category-

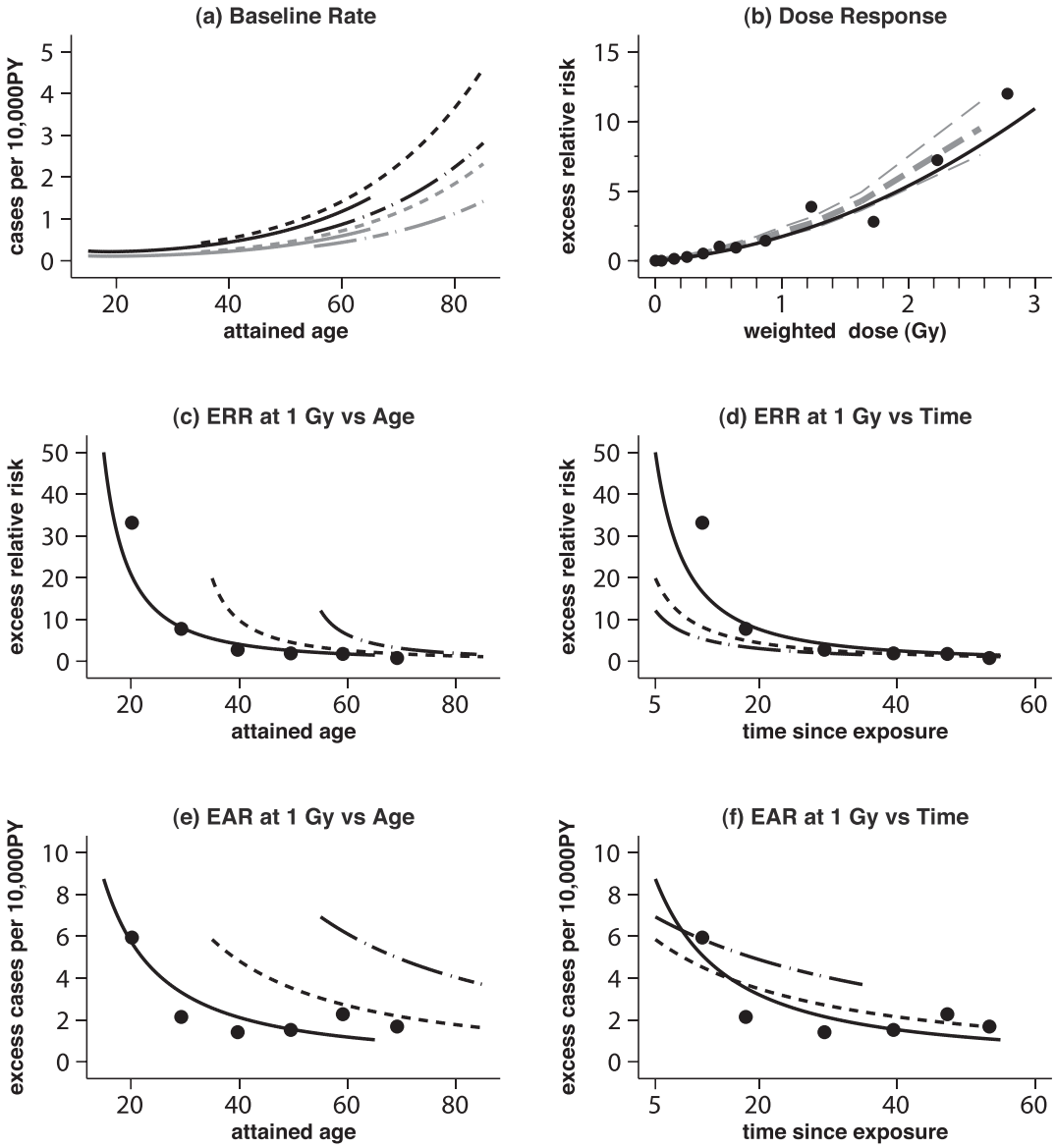

FIG. 1. Summaries of the risk of leukemia other than CLL or ATL in the LSS. Plot (panel a) shows age-specific baseline (zero dose) rates in Hiroshima for men (black lines) and women (gray lines) for LSS cohort members born in 1895 (dash-dot line; age at exposure 50), 1915 (dash line; age at exposure 30) and 1935 (solid line; age at exposure 10). Panel b: illustrates the radiation dose response based on the ERR model with risks standardized to attained age 70 for a person exposed at age 30 (born in 1915). The solid-black line illustrates the fitted linear-quadratic dose response. The points are based on a nonparametric dose-response model, while the middle-dashed-gray line is a smoothed version of the dose category-specific estimates from the nonparametric fit. The upper- and lower-dashed-gray line are plus and minus one standard error from the smoothed fit. Panels c and d: illustrate the temporal pattern and age-at-exposure effects for our preferred ERR model. The fitted ERR did not depend on either gender or city. Panels e and f: present the temporal pattern and age-at-exposure effects for Hiroshima males based on the preferred EAR model. The points in panels c–f are nonparametric estimates for exposure at age 10.

specific standardized ERR estimates and a dose-response function defined by smoothing the category-specific standardized estimates.

Based on our preferred ERR model (described below), it was estimated that about 94.1 of the 312 cases of leukemia other than CLL or ATL used in these analyses were associated with the radiation exposure (Table 2). The radiation-associated excess cases account for about 49% of the 192 cases among cohort members with doses in excess of 5 mGy.

Parameter estimates and confidence intervals for the preferred model for leukemia other than CLL or ATL are given in Table 3. The ERR was found to depend jointly on log attained age ($P < 0.001$) and either age at exposure ($P = 0.01$) or time since exposure ($P = 0.003$). These two models (age and age at exposure or age and time since exposure) led to similar patterns of the excess risk. However, since the fit of the age and time since exposure model (AIC = 2431.89) was somewhat better than that for the age and age at exposure model (AIC = 2433.97), our preferred model

TABLE 2
Observed and Fitted Cases of Leukemia Other than CLL or ATL by Weighted Bone Marrow Dose Categories

Dose (Gy)	Person years	Mean dose (Gy)	Observed cases	Fitted cases†	
				Background	Excess
<0.005	2,039,093	0.0006	120	116.9	0.1
–0.1	957,889	0.03	63	60.7	3.6
–0.2	201,935	0.14	16	13.7	4.1
–0.5	206,749	0.32	25	13.6	11.1
–1	117,855	0.71	24	7.5	18.2
–2	64,122	1.37	35	4.0	28.4
2+	25,761	2.68	29	1.5	28.6
Total	3,613,404	0.10	312	217.9	94.1

† Estimates based on the preferred ERR linear-quadratic model described in the text and Table 3 with additional details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

includes age and time since exposure as effect modifiers. As indicated in the upper portion of Table 3, with both of these temporal factors in the model, the decrease in the ERR with increasing attained age was proportional to attained age to the power −1.09 and simultaneously proportional to time since exposure to the power −0.81. The model predicted that the highest ERRs were seen shortly after exposure among those exposed early in life (Fig. 1d). However, due to the rapid decline in the ERR with time, at any given attained age the ERR was greater for those who were exposed at older ages (Fig. 1c). There was no indication that the ERR varied significantly with gender ($P = 0.29$) or city ($P = 0.42$), nor did it appear that the dose-response curvature varied with city ($P > 0.5$). The precise form of this model is indicated in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1) and information on the fit of alternative models is given in supplementary Table S6 (http://dx.doi.org/10.1667/RR2892.1.S2).

The excess absolute rates for leukemia other than CLL or ATL could also be described by a linear-quadratic EAR model in which the radiation-associated excess rate depended on attained age ($P < 0.001$), age at exposure ($P < 0.001$) and city ($P = 0.03$), with a suggestion of a statistically significant gender difference ($P = 0.08$). This EAR model (AIC = 2433.2) describes the data slightly worse than the preferred ERR model discussed above. An EAR model with log-time since exposure and age-at-exposure effects (AIC = 2,438.8) fit worse than the preferred attained age and age-at-exposure model. Adding attained age to this time-since-exposure model led to a statistically significant improvement in fit ($P < 0.001$). The resulting model was virtually identical to the attained-age model. Thus, attained age with an age-at-exposure effect provided a better description of the temporal variation of EAR than did attained age with a time-since-exposure effect.

In our preferred EAR model (Table 3 and supplementary Table S6: http://dx.doi.org/10.1667/RR2892.1.S2), the linear dose coefficient estimates (standardized to age 70 after exposure at age 30) in Hiroshima were 1.06 excess cases per 10,000 PY per Gy for men and 0.7 for women with estimated curvature similar to the ERR model. The decrease

TABLE 3
Preferred Model, Excess Risk Parameter Estimates for Leukemia Other than CLL or ATL

Risk model	Dose coefficients (at 1 Gy)		Curvature	Gender ratio (F:M)	City ratio (N:H)	Attained age (power)	Time since exposure (power)	Age at exposure
	Linear	Quadratic						
ERR†	0.79 (0.03, 1.93)	0.95 (0.34, 1.80)	1.20 (0.23, 49.35)			−1.09 (−2.01, −0.27)	−0.81 (−1.31, −0.28)	
EAR‡								
Women	0.70 (0.13, 1.53)	0.71 (0.24, 1.41)	1.03 (0.20, 8.52)	0.66 (0.41, 1.04)	0.52 (0.26, 0.93)	−1.45 (−2.13, −0.80)		0.41 (0.2, 0.64)
Men	1.06 (0.16, 2.42)	1.09 (0.37, 2.13)						

† The preferred ERR model is linear quadratic in dose with log-linear effect modification depending on log (attained age) and log (time since exposure). The baseline model parameters and explicit details about the dose effect modification term are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1). Supplementary Table S6 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on other ERR models. The dose coefficients describe the ERR at 1 Gy at age 70 after exposure at age 30.

‡ The preferred EAR model is linear-quadratic in dose with log-linear effect modification depending on log (attained age) and age at exposure. The baseline model parameters and explicit details about the dose effect modification term is given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1). Supplementary Table S6 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on other EAR models. The dose coefficients describe the excess cases per 10,000 person years at 1 Gy at age 70 after exposure at age 30.

TABLE 4
Observed and Fitted Excess Cases of Leukemia Other than CLL or ATL by Time Period and Age at Exposure with Category-Specific ERR Estimates

	Age at exposure									
	0–19		20–39		40+		Total			
Period	Obs	Exc[†]	Obs	Exc	Obs	Exc	Obs	Exc	ERR[‡] (95%CI)	
1950–1955	18	16.2	11	6.5	13	7.6	42	30.3	15.2	(8.8 to 25)
1956–1959	17	5.4	4	4.1	18	4.7	39	14.2	13.3	(7.2 to 23)
1960–1969	14	6.3	17	6.5	19	6.0	50	18.8	4.8	(2.3 to 8.4)
1970–1979	11	4.7	33	5.3	18	3.2	62	13.2	3.4	(1.5 to 6.3)
1980–1989	17	4.4	25	4.3	12	1.3	54	9.9	1.8	(0.5 to 3.8)
1990–2001	29	4.3	32	3.0	4	0.3	65	7.6	2.1	(0.8 to 4.3)
Total	106	41.3	122	29.7	84	23.1	312	94.0		
ERR[‡] (95% CI)	6.5 (4.0 to 10.3)		3.9 (2.3 to 6.1)		4.0 (2.1 to 6.9)		4.7 (3.3 to 6.5)			

[†] Excess cases based on preferred ERR model described in the text and Table 3 with additional details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

[‡] ERR at 1 Gy for a linear dose response model with categorical period or age at exposure effects.

in the EAR with attained age was proportional to age to the power −1.45, while the EARs for a given attained age were estimated to increase by about 51% per decade increase in age at exposure (95% CI 23–89%). Excess rates for Nagasaki survivors were estimated to be about 52% of those for Hiroshima survivors of the same gender and exposure age, and excess rate estimates for women were about 66% of those for men. The variation in the fitted EAR estimates with attained age and time since exposure for various ages at exposure are shown in Fig. 1e and f, respectively.

We used a simple ERR model with categorical main effects for six time periods and three age-at-exposure groups to examine whether or not the risks had persisted throughout the follow-up period. As indicated by the results summarized in Table 4, there was evidence of statistically significant increased risks in each of the six time periods considered. The largest ERRs were seen for the two earlier periods. However, even for the last 12 years of follow-up (1990–2001 or 45–55 years after exposure), the radiation-associated leukemia risk at 1 Gy was estimated to be twice the baseline risk.

Acute Myeloid Leukemia (AML)

There were 176 eligible AML cases, including 42 cases diagnosed after 1987 among LSS cohort members who were in the cities at the time of the bombings and 15 cases among cohort members who were NIC at the time of the bombings.

As indicated in Fig. 2a, AML baseline rates increased with attained age, but the level of risk and the nature of the increase with age differed for men and for women ($P < 0.001$). Baseline rates for women were about 40% (95% CI 29–56%) of those for men, and the rate of increase with attained age was more rapid for men than for women ($P = 0.04$). The baseline rates also exhibited a complex birth cohort effect. Age-specific rates were larger for people born between 1915 and 1925 than for people born before or after this period ($P < 0.001$). This pattern is similar to that seen in the Japanese national leukemia mortality rates, but somewhat more pronounced in the LSS cohort. The baseline AML rates in Nagasaki were 25% lower, though not significantly lower ($P = 0.14$), than those in Hiroshima. The AML baseline rate model and parameter estimates are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

Dose response and effect modification. There was strong evidence for a radiation dose-response relationship ($P < 0.001$). As shown in Fig. 2B, the dose-response curve was concave upward ($P = 0.01$). A pure-quadratic model with an estimated ERR at 1 Gy of 1.11 (95% CI 0.53–2.08, standardized to age 70 after exposure at age 30) as shown in Table 6 described the data as well as a linear-quadratic model ($P > 0.5$). Inference about effect modification in the ERR and EAR was based on a pure-quadratic model. In our preferred AML models (described below), the number of radiation-associated cases was estimated to be 37.4 (Table 5). The fraction attributable to radiation was 38% among cohort members with doses in excess of 5 mGy.

ERRs for AML exhibited a statistically significant [$P = 0.004$, with 2 degrees of freedom (*df*)] non-monotone dependence on age at exposure. As suggested in Fig. 2c, for any attained age (after exposure), the ERR for the people exposed around age 30 tended to be lower than for those exposed later or younger in life. The decrease in the ERR with attained age (AIC = 1,552.14) was well described as proportional to age to the power −0.89 (Table 6). More complex patterns for the age/time dependence were also considered. Neither the addition of a quadratic term in log age nor the use of splines in log age significantly improved the fit, nor did the use of functions of time since exposure result in better fits ($P > 0.5$ in every case). There was no indication of an attained age by age-at-exposure interaction ($P > 0.5$), nor did the attained age or age-at-exposure effects appear to vary with gender ($P > 0.5$). Parameter estimates with confidence intervals for the preferred AML,

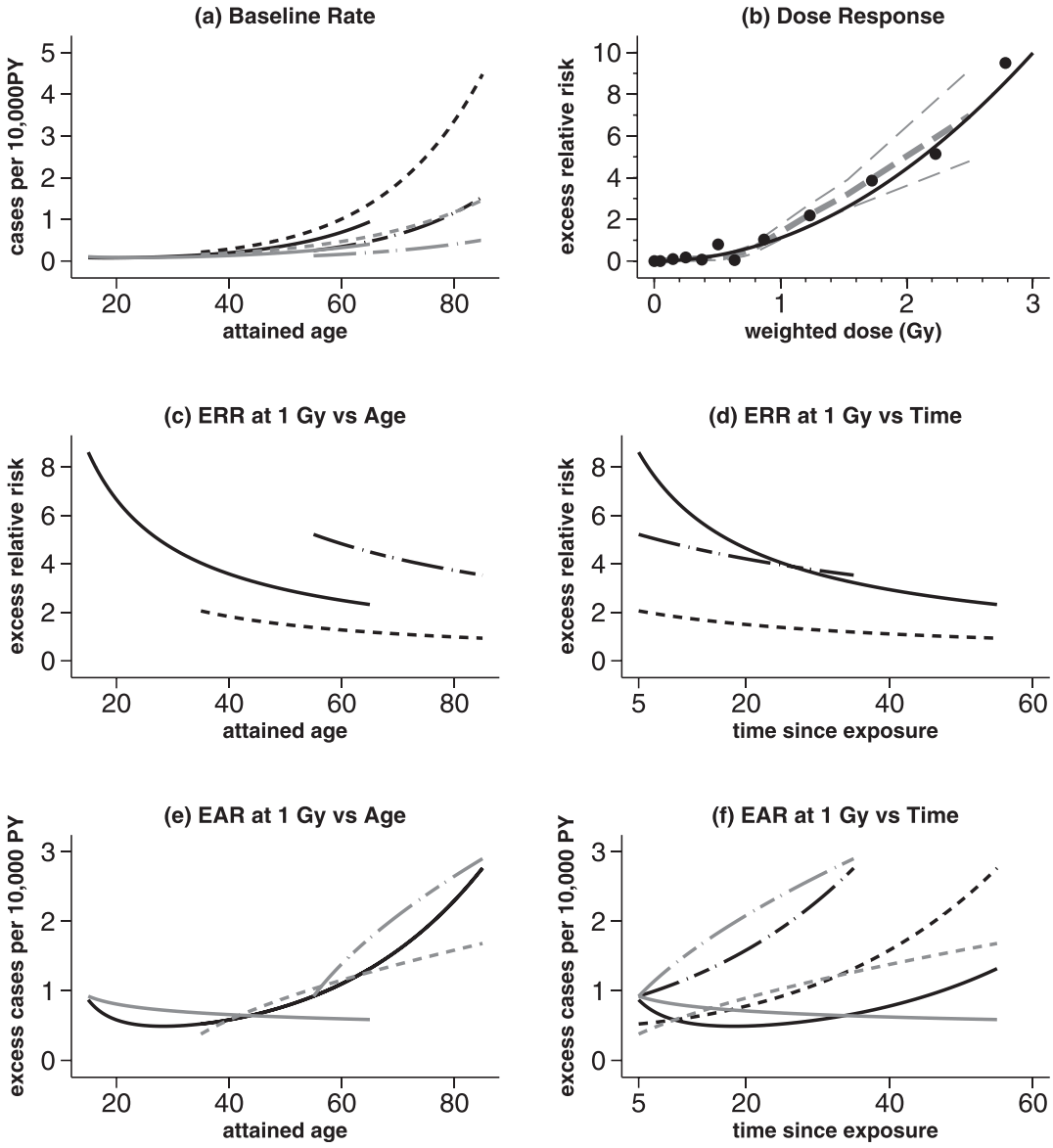

FIG. 2. LSS acute myeloid leukemia risk summary plots. Panel a: shows age-specific rates in the Hiroshima baseline (zero dose) for men (black lines) and women (gray lines) for LSS cohort members born in 1895 (dash-dot line; age at exposure 50), 1915 (dash line; age at exposure 30) and 1935 (solid line; age at exposure 10). Panel b: illustrates the radiation dose response based on the preferred ERR model with risks standardized to attained age 70 for a person exposed at age 30 (born in 1915). The solid-black line illustrates the fitted pure-quadratic dose response. The points are based on a nonparametric dose-response model, while the middle-dashed-gray line is a smoothed version of the dose category-specific estimates from the non-parametric fit. The upper- and lower-dashed-gray lines are plus and minus one standard error from the smoothed fit. Panels c and d: illustrate the temporal pattern and age-at-exposure effects for our preferred ERR model. Panels e and d: present the temporal pattern and age-at-exposure effects for Hiroshima males based on the preferred EAR model. Black lines are shown for ages at exposure of 10 (solid line), 30 (dash line) and 50 years (dash-dot line). The gray lines are the EAR temporal patterns using the model specified in a previous report (*4*). For the ERR and EAR models shown here, the excess risks did not depend on either gender or city.

ERR and EAR models are given in Table 6. Additionally, the precise form of this model is given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1) and information on the fit of alternative models is given in supplementary Table S7 (http://dx.doi.org/10.1667/RR2892.1.S2).

The AML EAR was also described equally well (AIC = 1,550.0) using a model with a linear-quadratic effect in log attained age. This description of the temporal pattern of the AML, which is illustrated in Fig. 2e, is considerably simpler than the model used in the previous LSS leukemia incidence report (*4*). In that model, there were separate temporal patterns for each of three age-at-exposure groups, while all of the temporal variation excess rates in the current model are expressed in terms of age without the need for dependence on either age at exposure or time since exposure. Figure 2e and f shows the variation of the AML EAR with attained age and time since exposure based on the

TABLE 5
Observed and Fitted Background and Excess Cases of Acute Myeloid Leukemia by Weighted Bone Marrow Dose Category

Dose (Gy)	Person years	Observed cases	Fitted cases†	
			Background	Excess
<0.005	2,039,093	77	75.6	0.0
–0.1	957,889	36	37.7	0.2
–0.2	201,935	9	8.2	0.6
–0.5	206,749	12	8.4	2.7
–1	117,855	11	4.9	6.9
–2	64,122	18	2.8	14.0
2+	25,761	13	1.0	13.0
Total	3,613,404	176	138.6	37.4

† Estimates based on the preferred quadratic ERR model described in the text and Table 6 with additional details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

current model together with using lighter lines, the pattern from an EAR model of the form used in the 1994 report. The new model predicts somewhat lower excess rates shortly after the bombings for those exposed as children, and somewhat higher rates throughout the follow-up for those exposed at age 50.

The fitted models illustrated in Fig. 2f reveal an upward trend in the AML excess rates in recent years, suggesting that excess risks have persisted throughout the entire follow-up period. Categorical analyses based on a simple model with main effects for three age-at-exposure and six period effects were used to assess the persistence of the risk. As seen in Table 7, there was evidence of increased risks in the last 12 years of follow-up with a significantly elevated ERR at 1 Gy of 1.5, representing about 6 excess cases during this period.

Acute Lymphoblastic Leukemia (ALL)

There were 43 eligible ALL cases. This relatively small number of cases, coupled with a large proportion (about half, described below) being associated with radiation exposure, makes it difficult to make precise inferences about the baseline rates. However, it appeared that ALL baseline rates increased with attained age ($P = 0.01$). This increase was estimated to be proportional to attained age to the power 1.70 (95% CI 0.34–3.36) (supplementary Table S2; http://dx.doi.org/10.1667/RR2892.1.S1), and allowing for more complex age patterns did not improve the fit. Population data for Japan and other countries (*34*) suggest that ALL baseline rates have a U-shaped pattern in which the rates reach a minimum in the 30–40 age range and increase at older ages. We did not find evidence for such a pattern in our data, most likely reflects the limited power due to the small number of cases in the cohort. There was no evidence of gender differences in either the level of risk ($P > 0.5$) or the age pattern ($P > 0.5$), nor were there any indications of a trend in the baseline rates with birth cohort ($P = 0.17$) or of city differences ($P = 0.43$). Figure 3a illustrates how the fitted baseline ALL rates vary with attained age. The ALL baseline rate model and parameter estimates are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

Dose response and effect modification. There was a significant linear dose-response relationship ($P < 0.001$) with some indication of upward curvature ($P = 0.05$), much of which was influenced by 4 cases with unweighted shielded kerma estimates in excess of 4 Gy. After adjusting for the high-dose cases by including a dichotomous indicator, there was no evidence of significant curvature ($P = 0.13$). Figure 3b shows the estimated linear dose response. In our preferred ALL model (described below), the number of radiation-associated ALL cases was estimated to be 21.6 (Table 8). About 67% of the cases among cohort members with doses in excess of 5 mGy were associated with radiation exposure.

The ERR for ALL decreased markedly over time ($P < 0.001$). This decrease was described as proportional to attained age to the power −3.51 (Table 9). The ERR for women was about 40% of that for men. This gender- and attained-age-dependent ERR model (AIC = 496.4) described the data better than a model that included joint effects of age at exposure (higher for younger ages) and time since exposure (decreasing with time) (AIC = 502.7). As illustrated in Fig. 3c, this model predicted extremely

TABLE 6
Preferred Model, Excess Risk Parameter Estimates for Acute Myeloid Leukemia

Risk model	Quadratic dose coefficient (at 1 Gy)	Attained age		Age at exposure	
		Linear	Quadratic	Linear	Quadratic
ERR†	1.11 (0.53, 2.08)	–0.89 (−2.29, 0.41)		0.17 (−0.15, 0.50)	0.25 (0.09, 0.41)
EAR‡	1.59 (0.95, 2.41)	2.59 (0.90,4.26)	1.43 (0.44, 2.32)		

† The preferred ERR model is quadratic in dose with log-linear effect modification depending on log(attained age) and a linear-quadratic function of age at exposure. The baseline model parameters and explicit details about the dose effect modification term are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1). Supplementary Table S7 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on alternative ERR models. The dose coefficients describe the ERR at 1 Gy at age 70 after exposure at age 30.

‡ The preferred EAR model is quadratic in dose with log-linear effect modification depending on a linear-quadratic function of log(attained age). The baseline model parameters and explicit details about the dose effect modification term is given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1). Supplementary Table S7 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on alternative EAR models. The dose coefficients describe the excess cases per 10,000 person years at 1 Gy at age 70.

TABLE 7
Observed and Fitted Excess Cases of Acute Myeloid Leukemia by Time Period and Age at Exposure with Category-Specific ERR Estimates

	Age at exposure									
	0–19		20–39		40+		Total			
Period	Obs	Exc†	Obs	Exc	Obs	Exc	Obs	Exc	ERR‡ (95%CI)	
1950–1955	4	3.1	3	0.7	4	2.5	11	6.4	3.6	(0.7 to 10.2)
1956–1959	7	1.3	3	0.7	8	2.2	18	4.2	9.0	(3.5 to 19.2)
1960–1969	7	2.1	7	1.7	10	3.9	24	7.7	3.1	(1.1 to 6.7)
1970–1979	7	2.3	21	2.1	13	2.4	41	6.8	1.9	(0.4 to 4.7)
1980–1989	12	3.0	20	2.2	7	1.1	39	6.3	1.8	(0.6 to 4.0)
1990–2001	19	3.9	23	1.9	1	0.3	43	6.1	1.5	(0.4 to 3.4)
Total	56	15.7	77	93	43	12.2	176	37.4		
ERR‡ (95% CI)	2.3 (1.0 to 4.5)		2.0 (0.9 to 3.8)		3.4 (1.5 to 6.6)		2.4 (1.5 to 3.7)			

† Excess cases based on preferred ERR model described in the text and Table 6 with additional details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

‡ ERR at 1 Gy for a quadratic dose response model with categorical period and age-at-exposure effects.

large ERRs for those exposed as children. Virtually all of the 22 cases among those exposed before age 20 could be attributed to radiation exposure.

The radiation effect on the ALL risk could be described equally well (AIC = 496.4) using an EAR model, as illustrated in Fig. 3e. In our preferred EAR model, the excess rate decreased in proportion to age to the power −1.81 (Table 9). There was a significant gender difference ($P = 0.05$) with an estimated female:male EAR ratio of 0.40. The gender-averaged EAR at age 70 was 0.16 radiation-associated cases per 10,000 person years per Gy (95% CI 0.05– 0.38). Parameter estimates with confidence intervals for the preferred ALL ERR and EAR models are given in Table 9. The precise form of this model is given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1) and information on the fit of alternative models is given in supplementary Table S8 (http://dx.doi.org/10.1667/RR2892.1.S2). The ALL EAR could be described almost as well using a combination of age-at-exposure and time-since-exposure effects in place of the attained age effect (supplementary Table S8; http://dx.doi.org/10.1667/RR2892.1.S2).

Both the ERR and EAR results indicated that the radiation-associated risks have decreased over time, but also suggested that dose-related increased risks may persist for many years after exposure. Using a simple ERR model in which the dose response was allowed to differ for the three periods of October 1950 through December 1952, 1953–1965 and 1966–2001, we found statistically significant dose-related increases in the risk for each period. Although the ERR decreased over time, the ERR for the last period was statistically significant and had a population average 3.1 (95% CI 0.6–10.4, $P = 0.001$) (results not shown).

Chronic Myeloid Leukemia (CML)

There were 75 eligible CML cases (63 in Hiroshima, 12 in Nagasaki) including 13 cases that occurred after 1987. The CML baseline rate increased with attained age ($P < 0.001$) with a significant difference in the age pattern for men and women ($P = 0.004$) (Fig 4a). Baseline rates for men were higher than those for women prior to age 75, but women had higher rates later in life, because the rates for women rose more rapidly than those for men. There was no indication of a birth cohort effect ($P > 0.5$). After allowing for a city difference in the dose response (described below), the baseline rates did not differ significantly by city ($P > 0.5$). The CML baseline rate model and parameter estimates are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

Dose response and effect modification. CML rates exhibited a statistically significant ($P < 0.001$) linear dose-response relationship that was not improved by the addition of a quadratic term ($P > 0.5$). The dose-response curve is shown in Fig. 4b. In our preferred ERR model for CML, the ERR was dependent on city and both time since exposure and attained age. As shown in Table 11, the estimated ERR was 5.24 per Gy standardized to attained age 55 and 25 years after exposure, and the ERR in Nagasaki was estimated to be 22% of that in Hiroshima ($P = 0.01$). There was no indication that the ERR differed by gender ($P > 0.5$).

The ERR decreased significantly in proportion to time since exposure to the power −1.59 at any attained age. The ERR decreased significantly in proportion to attained age to the power −1.42. Using the preferred ERR model the observed number of radiation-associated cases was estimated to be 33.4 with the attributable fraction among those exposed to 5 mGy or more estimated to be 64% (Table 10). Parameter estimates with confidence intervals for the preferred CML ERR and EAR models are given in Table 11, respectively. The precise form of this model is given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1). Figure 4c and d illustrate the temporal pattern for the Hiroshima ERR for this model as a function

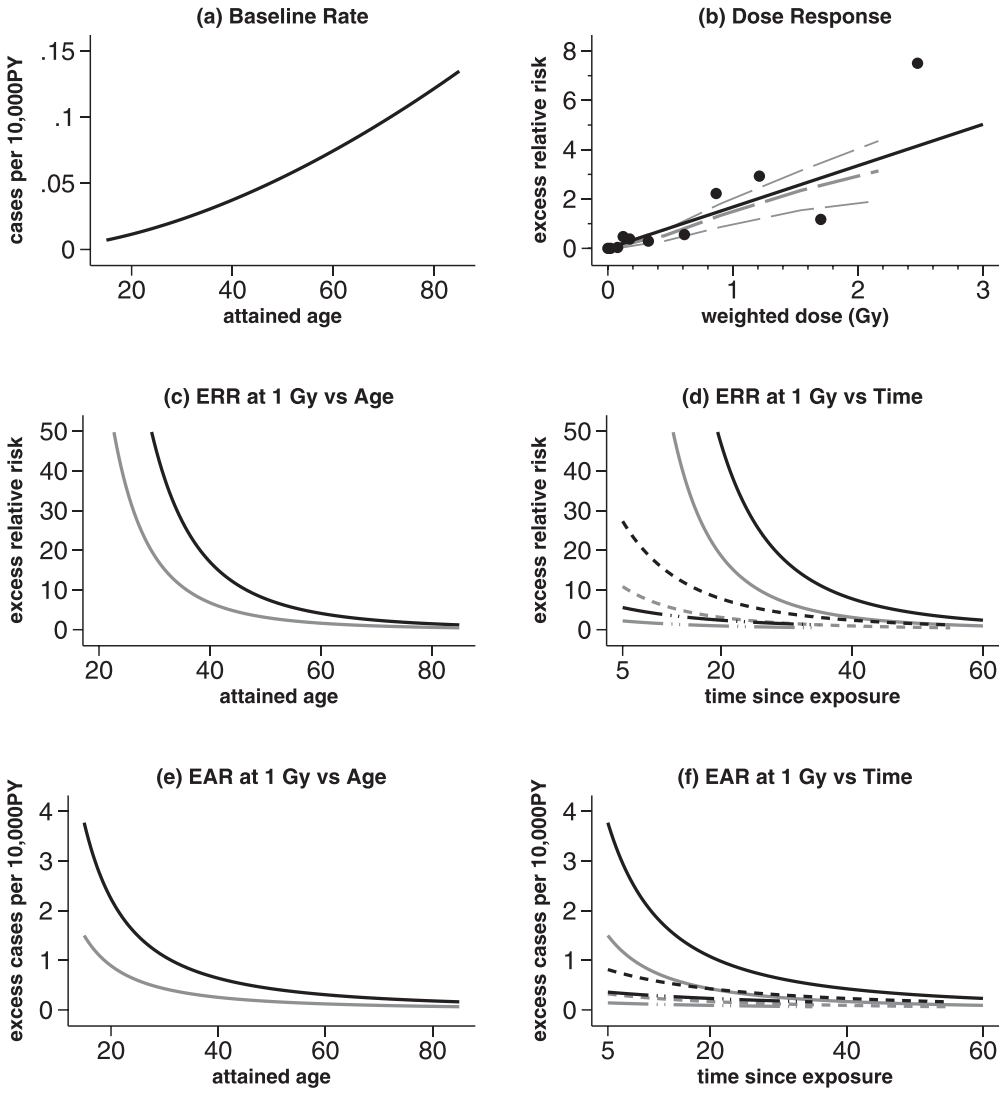

FIG. 3. LSS acute lymphoblastic leukemia risk summary plots. Panel a: shows age-specific Hiroshima baseline rate for LSS cohort members. Panel b: illustrates the radiation dose response based on the ERR model with gender average risks standardized to attained age 70. The solid-black line illustrates the fitted linear dose response. The points are based on a nonparametric dose response model, while the middle-dashed-gray line is a smoothed version of the dose category-specific estimates from the nonparametric fit. The upper- and lower-dashed-gray lines are plus and minus one standard error from the smoothed fit. Panels c and d: exhibit the temporal patterns for men (black line) and for women (gray line) in either city based on the preferred ERR model. Plots (e) and (f) present the temporal pattern for males (black) and females (gray) based on the preferred EAR model. In panels e and f: different line patterns are shown for ages at exposure of 10 (solid line), 30 (dash line) and 50 years (dash-dot line).

of attained age and time since exposure for exposure ages of 10, 30 and 50 years, respectively.

A model in which the ERR varied jointly with age at exposure, time since exposure and city (AIC = 777.7) described the data as well as the attained age, time since exposure and city model described above (AIC = 776.4). However, a model in which the ERR varied with attained age, age at exposure and city fit less well (AIC = 782.0). Parameter estimates and AIC values for these and other alternative models for the CML excess risk are given in supplementary Table S9 (http://dx.doi.org/10.1667/RR2892.1.S2).

In our preferred EAR model, the excess rate depended on city, time since exposure and a gender-dependent attained age effect. The gender-averaged EAR at age 55 after exposure at age 30 was 0.62 cases per 10,000 PY per Gy (95% CI 0.27–1.15). Excess rates for Nagasaki were about 23% of those in Hiroshima ($P = 0.01$). Figure 4e and f show the CML EAR temporal trends by gender and different age-at-exposure groups based on the preferred EAR model. For a given age at exposure, the decrease in the EAR was proportional to time since exposure to the power -1.63 ($P < 0.001$). The attained age effect differed significantly for men and women ($P = 0.01$). For any given time since exposure, the EAR for men exhibited little variation with attained age, decreasing in proportion to attained age to the power -0.20 ($P > 0.5$). Conversely, for women the EAR increased significantly ($P = 0.009$) with

TABLE 8
Observed and Fitted Background and Excess Cases of Acute Lymphoblastic Leukemia by Weighted Bone Marrow Dose Category

Dose (Gy)	Person years	Observed cases	Fitted cases†	
			Background	Excess
<0.005	2,039,093	11	12.0	0.06
–0.1	957,889	8	5.7	1.6
–0.2	201,935	4	1.2	1.6
–0.5	206,749	2	1.3	3.4
–1	117,855	5	0.7	4.0
–2	64,122	5	0.4	4.5
2+	25,761	8	0.1	6.4
Total	3,613,404	43	21.4	21.6

† Estimates based on the preferred linear ERR model described in the text and Table 9 with more details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

increasing attained age. This increase was proportional to attained age to the power 2.10. The preferred EAR (AIC = 779.7) and ERR model (AIC = 776.4) described the data about equally well.

Joint Analysis of AML, ALL and CML Dose Response

The results described provide clear evidence of a time-varying radiation dose response for AML, ALL and CML. As noted in the text and illustrated in Figs. 2, 3 and 4, the temporal patterns and shapes of the dose response appear to differ for these three broad leukemia subgroups. We carried out a joint analysis using the methods described in refs. (*4*) and (*35*) to formally examine the evidence for differences in the nature of the temporal patterns and shapes of the dose response for these three subgroups.

When the subgroups are fit with group-specific baseline rates and the linear-quadratic ERR model developed for all leukemias other than CLL or ATL (''common model''), the AIC was 2,848.8. This is considerably larger than the AIC of 2,825.0 obtained using the preferred subgroup-specific models described above. For EAR models, the AIC using the common EAR model was 2,858.1, while the AIC based on the preferred subgroup-specific EAR models was 2,827.5. Although a formal test of statistical significance is not possible, based on a comparison of the differences between the AICs for the common and group-specific models, there is a clear indication of subgroup differences for both the ERR and EAR models.

In the ERR model, there is evidence of significant heterogeneity relative to the common model with regard to variation in the risk with attained age ($P = 0.01$), time since exposure ($P = 0.004$) and city ($P = 0.03$). When the effect modification was allowed to have the form of the preferred model in each subgroup, there was little evidence of significant inter-subgroup variability in the dose-response curvature ($P = 0.14$).

Test for heterogeneity in EAR effect modification relative to the common EAR model indicates some evidence of heterogeneity with regard to gender ($P = 0.04$). After allowing for gender variation, there is evidence of heterogeneity with regard to time-since-exposure ($P = 0.01$) or age-at-exposure ($P = 0.04$) effects. As with the ERR model, there was little evidence of significant inter-subgroup variability in the dose-response curvature ($P = 0.17$).

Table 12 contains estimates of the possible number of radiation-associated excess cases by time period (for all age-at-exposure groups together) based on the preferred ERR models for AML, ALL and CML. The largest number of excess cases was seen during the first 5 years of follow-up. Table 12 also provides information on the within-period distribution of the excess over the three subtypes considered here. It can be seen that, while most of the excess cases in the 1950–1955 period are CML, as time has gone on AML has come to account for most of the excess.

Chronic Lymphocytic Leukemia (CLL)

CLL is rare in Japan. In the previous report, there were only four CLL cases, which were analyzed with the other leukemias. With additional follow-up time, 12 CLL cases

TABLE 9
Preferred Model, Excess Risk Parameter Estimates for Acute Lymphoblastic Leukemia

Risk model	Linear dose coefficient (at 1 Gy)	Gender ratio (F:M)	Attained age (power)
ERR† Female	0.95 (0.23, 3.37)	0.40 (0.14, 0.99)	–3.51 (−5.29, −1.92)
Male	2.40 (0.63, 7.90)		
EAR‡ Female	0.09 (0.03, 0.25)	0.40 (0.14, 0.99)	–1.81 (−2.56, −1.08)
Male	0.23 (0.07, 0.58)		

† The preferred ERR model is linear in dose with log-linear effect modification depending on log (attained age) and gender. The baseline model parameters and explicit details about the dose effect modification term are given in Table S2 in the supplementary material (http://dx.doi.org/10.1667/RR2892.1.S1). Supplementary Table S8 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on alternative ERR models. The dose coefficients describe the ERR at 1 Gy at age 70.

‡ The preferred EAR model is linear in dose with log-linear effect modification depending on log (attained age) and gender. The baseline model parameters and explicit details about the dose effect modification term are given in Table S2 in the supplementary material (http://dx.doi.org/10.1667/RR2892.1.S21). Supplementary Table S8 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on alternative EAR models. The dose coefficients describe the excess cases per 10,000 person years at 1 Gy at age 70.

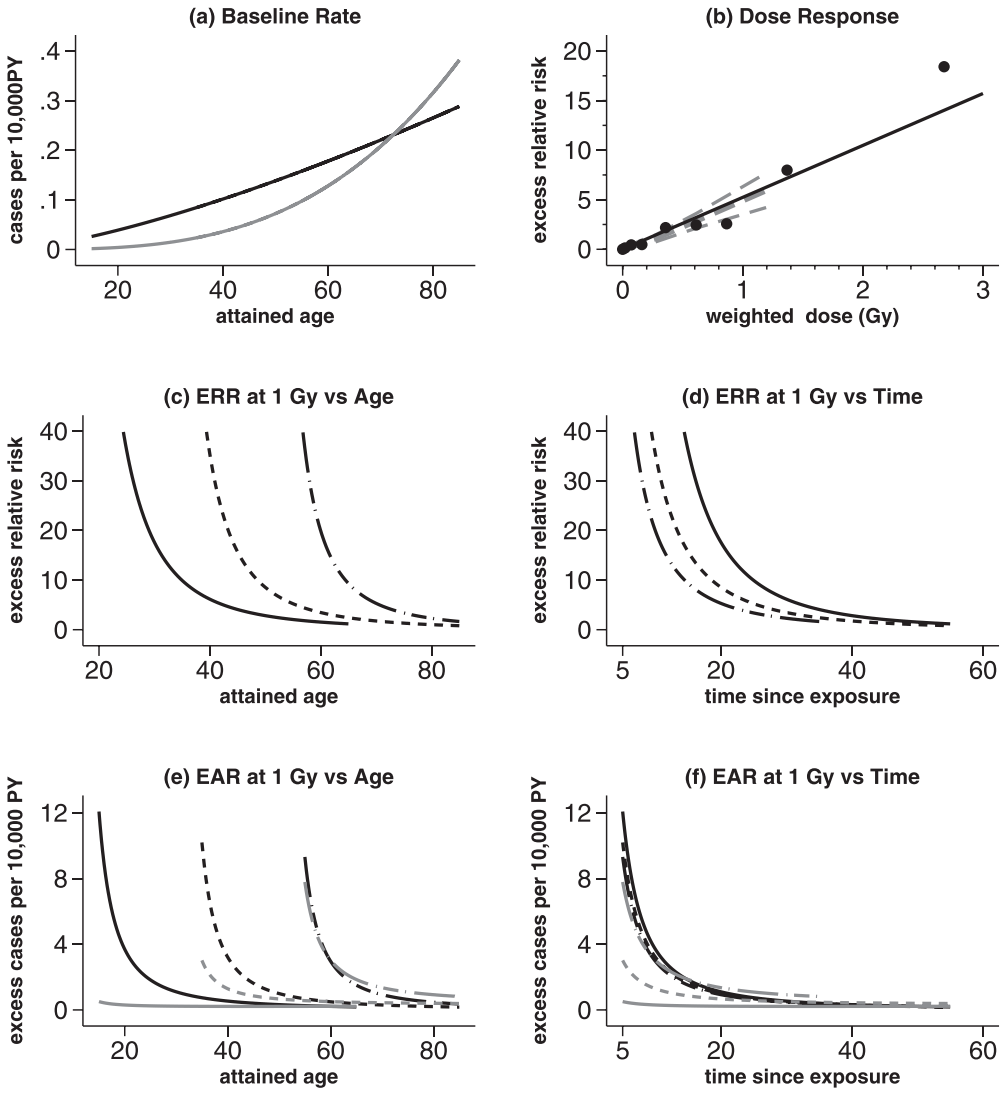

FIG. 4. LSS chronic myeloid leukemia risk summary plots. Panel a: shows age-specific Hiroshima baseline rate for LSS cohort members for men (black line) and women (gray line). Panel b: illustrates the radiation dose response based on the ERR model with gender average risks standardized to time since exposure at 25 and at attained age 55. The solid-black lines illustrates the fitted linear dose response. The points are based on a nonparametric dose response model, while the middle-dashed-gray line is a smoothed version of the dose category-specific estimates from the nonparametric fit. The upper- and lower-dashed-gray lines are plus and minus one standard error from the smoothed fit. Panels c and d: illustrate the temporal pattern and age-at-exposure effects for our preferred ERR model. Curves are shown for ages at exposure 10 (solid curve), 30 (dash line) and 50 years (dash-dot line) in Hiroshima. The ERR does not depend on gender. Panels e and f: present the temporal pattern and age-at exposure effects by gender based on the preferred EAR model in Hiroshima. Curves are shown for age at exposure 10 (solid line), 30 (dash line) and 50 years (dash-dot line) with black and gray lines for men and for women, respectively.

were identified including 10 cases classified as chronic lymphocytic leukemia and 2 as hairy cell leukemia. The newly identified cases included only one case among the not-in-city cohort members and 7 cases diagnosed after 1987. Using a simple age- and gender-adjusted baseline model, a significant linear dose response was detected, which suggested that CLL risk might be increased at higher doses ($P < 0.05$).

Adult T-Cell Leukemia (ATL), Nagasaki Only

There were a total of 47 eligible ATL cases. Due to the fact that there were only 5 ATL cases in Hiroshima, the analyses were limited to Nagasaki. The background rate exhibited a rapid increase with attained age that was proportional to the power 4.07 (95% CI 2.59–5.74, $P < 0.001$). Age-specific ATL rates in Nagasaki have changed significantly over time ($P = 0.01$), with rates estimated to have increased by about 34% for each decade increase in the year of birth (95% CI 7–71%). There were no statistically significant gender differences in the ATL baseline rates ($P > 0.5$). Figure 5 shows the increasing rates of ATL by age. The ATL baseline rate model and parameter estimates are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

TABLE 10
Observed and Fitted Background and Excess Cases of Chronic Myeloid Leukemia by Weighted Bone Marrow Dose Category

Dose (Gy)	Person years	Observed cases	Fitted cases†	
			Background	Excess
< 0.005	2,039,093	22	22.5	0.1
0.1	957,889	17	11.6	2.9
0.2	201,935	2	2.5	3.0
0.5	206,749	11	2.6	6.5
1	117,855	6	1.4	7.5
2	64,122	9	0.7	7.5
2+	25,761	8	0.3	5.9
Total	3,613,404	75	41.6	33.4

† Estimates based on the preferred linear ERR model described in the text and Table 11 with more details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

Dose response and effect modification. There was no evidence of a dose response for ATL ($P > 0.5$) and the ERR/Gy in a linear model was estimated as 0.05 (95% CI −0.51–1.54). Because of a lack of cases among women who received high doses, the ERR/Gy for women was estimated to be les than zero. After restricting the excess risk for women to be zero, the fit of the model was improved and the ERR/Gy estimate for men was 0.88 (95% CI −0.60–4.52, $P = 0.28$), which was not statistically significant.

Lymphoma

The 437 eligible lymphoma cases include 402 NHL and 35 HL cases with 143 of these cases diagnosed since 1987 among cohort members who were in the cities at the time of the bombings. Another 102 cases were among cohort members who were not in the cities at the time of bombings. NHL and HL risks were analyzed separately.

Non-Hodgkin lymphoma (NHL). Background rates for NHL increased rapidly with attained age. While this increase was roughly proportional to attained age to the fourth power, the fit was significantly improved when the nature of the increase was allowed to vary with increasing age, with knots at age 40 and 70 ($P = 0.007$, with 3 *df*). Age-specific rates for women were 58% of those for men (95% CI 48–72%, $P < 0.001$) with no significant ($P > 0.5$) gender difference in the nature of the increase with attained age. NHL baseline rates also exhibited a complex nonlinear birth cohort effect ($P < 0.001$) with the highest age-specific rates for cohort members born around 1940 and lower age-specific rates for people born in earlier or later years. As shown in Fig. 6a, the age-specific baseline rates for the 1935 birth cohort were at least twice those for the 1895 birth cohort. This pattern was similar to that seen for the LSS leukemia baseline rates and for Japanese national NHL rates (*33*). There was no indication of a city difference in the baseline rates ($P > 0.5$). The NHL baseline rate model and parameter estimates are given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

Dose response and effect modification. There was no evidence of a significant dose response in the ERR ($P = 0.23$) in a simple linear dose-response model. However, when the ERR was allowed to differ for men and women, there was a suggestion of an elevated risk in men (ERR/Gy = 0.46; 95% CI −0.08 to 1.29, $P = 0.11$), but no indication of an effect for women (ERR/Gy = 0.02; 95% CI <–0.44 to 0.64, $P > 0.5$). Allowing the ERR for men to vary with attained age led to a significant improvement in the fit relative to a model with no radiation effects ($P = 0.005$, with 2 *df*). Thus, while there was some evidence of a statistically

TABLE 11
Preferred Model, Excess Risk Parameter Estimates for Chronic Myeloid Leukemia

Risk model		Linear dose coefficient (at 1 Gy)	City ratio (N:H)	Gender ratio (F:M)	Attained age (power)	Time since exposure (power)
ERR†	Hiroshima	5.24 (1.92, 11.8)	0.22 (0.03, 0.75)		−1.42 (−3.04, 0.01)	−1.59 (−2.34, −0.95)
	Nagasaki	1.17 (−0.10, 4.71)				
EAR‡	Female	0.57 (0.23, 1.10)	0.23 (0.03, 0.76)	0.84 (0.34, 2.21)	2.10 (0.48, 4.21)	−1.63 (−2.38, −0.97)
	Hiroshima					
	Nagasaki	0.13 (<0, 0.47)				
	Male	0.68 (0.24, 1.49)			−0.20 (−1.03, 0.66)	
	Hiroshima					
	Nagasaki	0.15 (<0, 0.60)				

† The preferred ERR model is linear in dose with log-linear effect modification depending on log (attained age), log (time since exposure) and city. The baseline model parameters and explicit details about the dose effect modification term are given in Table S2 in the supplementary material (http://dx.doi.org/10.1667/RR2892.1.S21). Supplementary Table S9 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on alternative ERR models. The dose coefficients describe the ERR at 1 Gy at age 55 after exposure at age 30.

‡ The preferred EAR model is linear in dose with log-linear effect modification depending on city, sex, log(time since exposure) and log(attained age) with the attained age effect differing in the two cities. The baseline model parameters and explicit details about the dose effect modification term is given in Table S2 in the supplementary material (http://dx.doi.org/10.1667/RR2892.1.S1). Supplementary Table S9 (http://dx.doi.org/10.1667/RR2892.1.S2) presents information on alternative EAR models. The dose coefficients describe the excess cases per 10,000 person years at 1 Gy at age 55 after exposure at age 30.

TABLE 12
Radiation-Associated Excess Leukemia Cases by Subtype and Period

	Leukemia subtype†						
	AML		ALL		CML		
Period	Excess‡	Percent§	Excess	Percent	Excess	Percent	Total
1950–1955	6.3	20%	8.3	27%	16.3	53%	30.9
1956–1960	4.3	29%	4.1	28%	6.2	43%	14.6
1961–1970	7.6	43%	4.5	25%	5.7	32%	17.8
1971–1980	6.8	57%	2.4	20%	2.7	23%	11.9
1981–1990	6.2	68%	1.4	15%	1.5	17%	9.1
1991–2001	6.1	78%	0.8	10%	0.9	12%	7.8
Total	37.3	41%	21.5	23%	33.3	36%	92.1

† The subtypes considered here are acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML).

‡ Radiation-associated excess case estimates based on the preferred ERR models described in the text and in Tables 6, 9 and 11 with additional details given in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

§ Percentage of radiation associated excess cases within the time period.

significant radiation effect in men, there was no indication of a radiation effect in women.

As indicated by the dose-response curves in Fig. 6c, the ERR/Gy for men (dark solid curve) was large at younger ages, but declined dramatically and approached 0 by age 40. It is difficult to interpret the large ERRs for the very young since baseline rates are highly variable and imprecise due to the small number of children and young adults at risk for developing NHL. The EAR model provided a more simple and perhaps more useful description for small excess risks when baseline rates are low. There was a suggestion of a dose response ($P = 0.10$) in a simple constant EAR model. Letting the EAR depend on gender led to a significant improvement in the fit ($P = 0.048$). The estimated EAR for men was 0.54 (95% CI 0.09–1.32, $P = 0.003$) while that for women was essentially 0 (95% CI −0.02–0.31, $P > 0.5$). There was no indication that the EAR varied with attained age ($P = 0.3$), time since exposure ($P = 0.46$), or age at exposure ($P = 0.15$). Supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S21) contains information on the form of the final model than the parameter estimates for this model.

Figure 6d presents the fitted constant EAR for men (dark solid line) and the EAR estimate derived from the age-dependent ERR model (lighter dashed line) described above. While the EAR model suggested a persistent increase in risk, the ERR model suggested that the excess rate peaked around age 20 and that there was little excess after age 30, which also implies that the radiation effects were seen primarily among those exposed as children or young adults. Despite striking differences in the pattern of the excess risk, the goodness of fit of the ERR (AIC = 2,374.8) and EAR (AIC = 2,378.8) models was comparable. Based on the time-constant EAR model, the estimated number of radiation-associated cases over the follow-up period was estimated to be 7.8 for men and 0 for women (Table 13), with about 10% of the cases among men with doses in excess of 5 mGy attributable to the radiation exposure. The time-dependent ERR model predicts about half the number of excess cases as does the EAR model.

Hodgkin Lymphoma (HL)

There were only 35 eligible HL cases in the cohort. Age- and birth-cohort adjusted baseline rates in women were about 40% of those in men (95% CI 21–82%, $P = 0.01$). Baseline rates tended to increase with increasing attained age, but the increase was not statistically significant ($P = 0.35$). However, age-specific rates in later birth cohorts were significantly lower than those for earlier birth cohorts ($P = 0.003$). There was no indication of a city difference in the baseline rates ($P = 0.16$). HL baseline rates are plotted in Fig. 7. The HL baseline rate model and parameter estimates are described in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1).

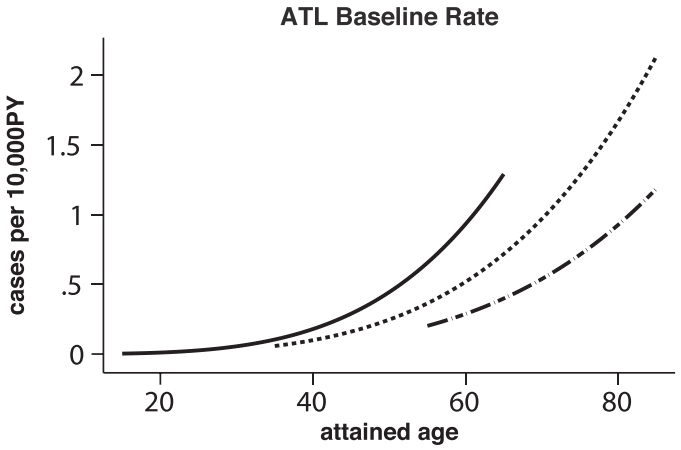

FIG. 5. LSS adult T-cell leukemia risk summary plots. The plot shows age-specific Nagasaki baseline rates (zero dose) for LSS cohort members born in 1895 (dash-dot line), 1915 (dash line) and 1935 (solid line). There is no significant dose response.

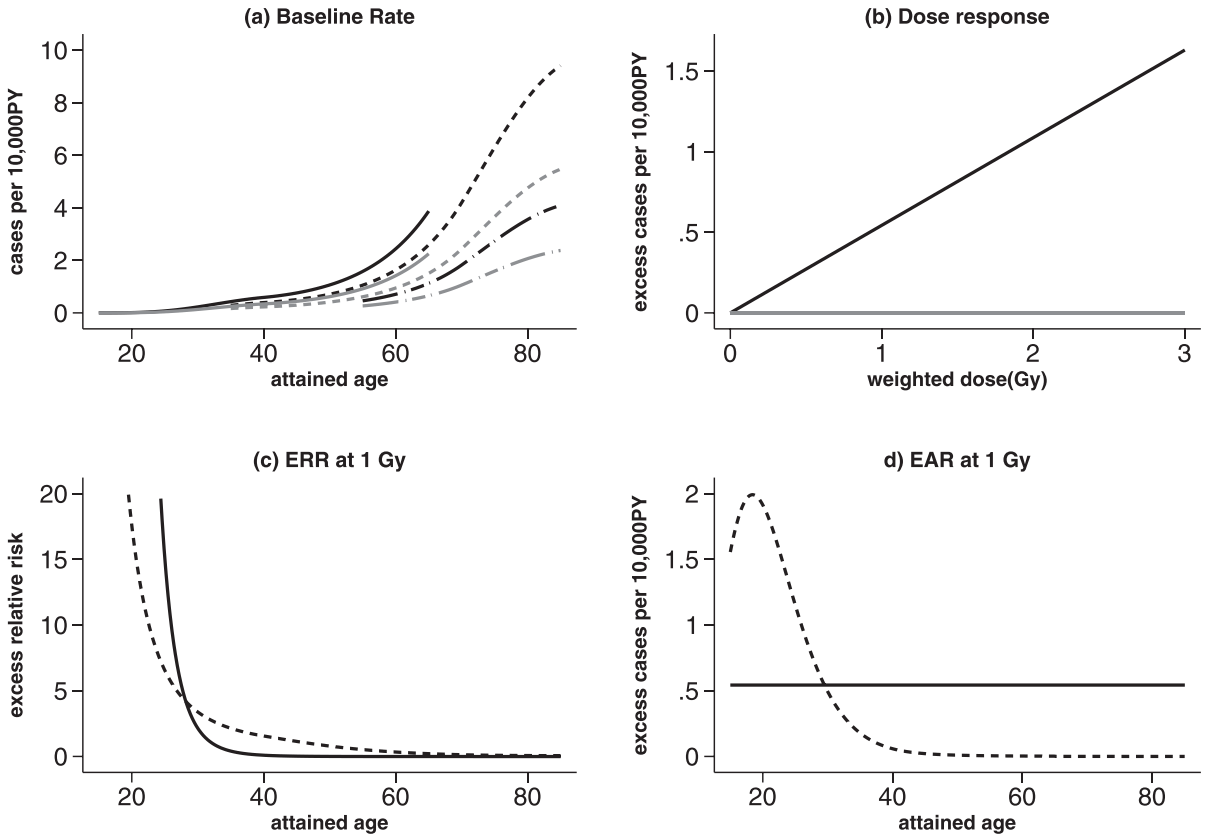

FIG. 6. LSS non-Hodgkin lymphoma risk summary plots. Panel a: shows age-specific Hiroshima baseline rates for LSS cohort members. Curves are shown for birth cohorts 1895 (dash-dot line), 1915 (dash line) and 1935 (solid line) model with black and gray lines for men and for women, respectively. Panel b: illustrates the radiation dose response based on the EAR model with black and gray lines for men and for women, respectively. Panel c illustrates the ERR temporal pattern for men. The solid line shows the predicted ERR based on our preferred ERR model, and the dotted line is the ERR derived from our preferred EAR model. Panel d: presents the EAR temporal pattern for men. The dotted line shows the predicted EAR based on our preferred EAR model and the solid curve is the EAR derived from our preferred ERR model.

Dose response and effect modification. No significant dose response was found for HL (ERR/Gy = 0.20; 95% CI −1.03–2.63, $P > 0.5$). Allowing the dose response to depend on gender did not improve the fit of the model ($P > 0.5$), nor was there any indication of statistically significant variation in the ERR with age ($P > 0.5$). The estimated time constant EAR was essentially 0 ($P > 0.5$).

Multiple Myeloma (MM)

Among the 181 cases of MM identified in this study, 136 were eligible for use in the risk analyses including 36 cases diagnosed in survivors after 1987 and 31 cases diagnosed among cohort members who were not in the cities at the time of the bombings.

Baseline rates varied significantly with both attained age ($P < 0.001$) and birth cohort ($P < 0.001$). The birth cohort effect appeared to be non-monotonic, with the largest age-specific rates seen for people born around 1920 and decreasing by about 35% per decade for earlier and later birth cohorts. This pattern was generally similar to that seen in leukemia other than CLL or ATL in this cohort. The increase in rates was roughly proportional to attained age to the power 5.45 (95% CI 4.41–6.55, $P < 0.001$). However, the model was significantly improved ($P = 0.01$) when the baseline rate was allowed to increase to about age 80 and level out, or even decrease later in life (Fig. 8).

TABLE 13
Observed and Fitted Background and Excess Cases of Non-Hodgkin Lymphoma Cases by Weighted Bone Marrow Dose Category

Dose (Gy)	Person years	Observed cases	Fitted cases†	
			Background	Excess
<0.005	2,039,093	226	221.6	0.02
–0.1	957,889	99	104.2	0.6
–0.2	201,935	21	22.7	0.6
–0.5	206,749	28	22.9	1.3
–1	117,855	13	13.2	1.7
–2	64,122	14	7.1	2.0
2+	25,761	1	2.5	1.6
Total	3,613,404	402	394.2	7.8

† Estimates based on the preferred linear EAR model described in the text with additional details in supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1). This is gender-dependent, time-constant linear EAR model with an EAR of 0.54 cases per 10,000 PY at 1 Gy and no excess risk for women.

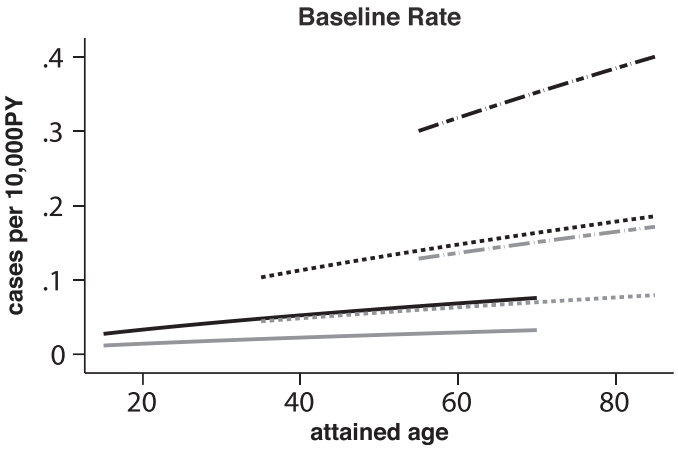

FIG. 7. LSS Hodgkin lymphoma. The plot shows age-specific baseline rates (zero dose) for LSS cohort members born in 1895 (dash-dot line), 1915 (dot line) and 1935 (solid line). The black lines are for men and the gray lines are for women. There is no significant dose response.

The background risk did not vary significantly with either gender ($P = 0.16$) or city ($P = 0.12$). Supplementary Table S2 (http://dx.doi.org/10.1667/RR2892.1.S1) contains information on the form of the final baseline rate model with the associated parameter estimates.

Dose response and effect modification. The ERR/Gy estimate of 0.38 from a linear dose-response model was not statistically significant (95% CI −0.23–1.36, $P = 0.21$) The fit was not improved by the addition of a quadratic term ($P = 0.44$). There was no evidence of statistically significant variation in the ERR with gender ($P > 0.5$), attained age ($P = 0.31$) or age at exposure ($P > 0.5$).

When the data were described using a constant linear EAR model, the estimated EAR was 0.07 cases per 10,000 PY per Gy (95% CI <–0.05–0.29, $P = 0.25$), with no indication of variation with gender ($P = 0.5$), attained age ($P = 0.33$) or time since exposure ($P > 0.5$). This point estimate of the EAR is almost identical to that reported 15 years ago. As in the previous report, we conclude that there is no evidence of a statistically significant radiation-associated excess risk of incident MM in the atomic bomb survivors.

DISCUSSION

Our study extends the follow-up 14 years beyond that used in the last major report on hematological malignancies in the LSS cohort (*4*), providing incidence follow-up for 55 years. This has been made possible because of the active ascertainment and review of hematopoietic malignancies already in place when the cohort was established in late 1950, together with the subsequently established tumor registries in Hiroshima and Nagasaki. Due to incomplete ascertainment of incident cases among cohort members who moved away from Hiroshima or Nagasaki, a probabilistic adjustment for migration was included in the analyses as with all other major LSS incidence reports. Diagnostic criteria and type definitions for hematopoietic malignancies have evolved and been refined over time, but the reclassification of leukemia types for cases diagnosed before the mid-1980s using the recent classifications has enabled us to use diagnostic categories that are consistent with and generally as detailed as those used in other studies of radiation effects on these malignancies.

In contrast to the earlier report (*4*) that focused exclusively on time-since-exposure dependent EAR models with, in most cases, categorical age-at-exposure effects, we assessed excess risk in this report using ERR and EAR models with simple continuous functions of age at exposure and either attained age or time since exposure. We found that those smooth models describe the data as well as the partially categorical models used in ref. (*4*). We also found that while both ERRs and EARs for leukemia other than CLL or ATL as a group have declined over the follow-up period for all ages at exposure (Fig. 1d and f), the excess risks do not appear to have fallen to zero by the end of the follow-up—55 years after exposure. The temporal variation of either the ERR or EAR as described in terms of (post-

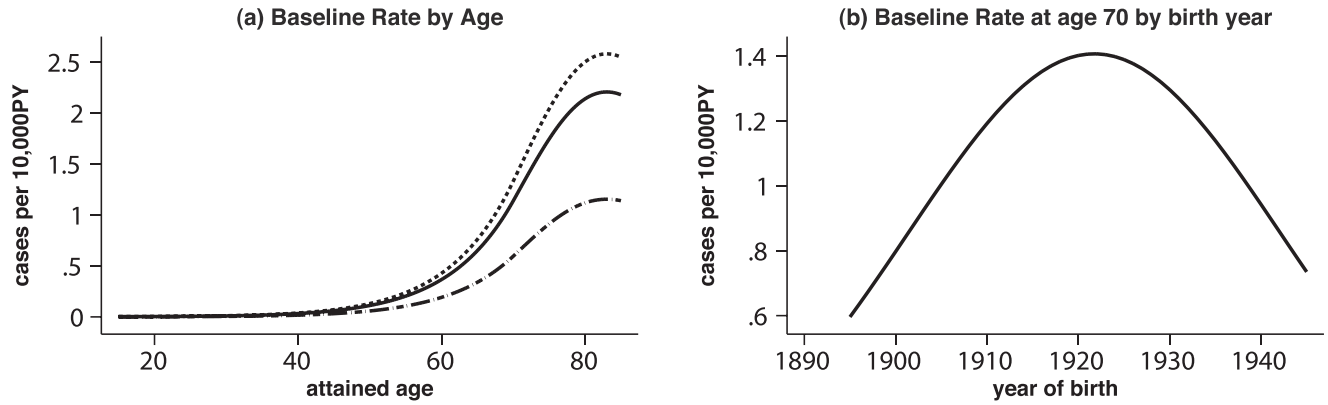

FIG. 8. LSS multiple myeloma summary plots. Panel a: shows age-specific baseline rate (zero dose) for LSS cohort members born in 1895 (dash-dot line), 1915 (dash line) and 1935 (solid line). Panel b: shows the baseline rate by birth year at attained age 70.

TABLE 14
Comparison of Risk Estimates to Selected Cohort Studies

Study cohort	Cancer end point	Follow-up	Cases	Average dose (range)	Dose response model	ERR: Leukemia excluding CLL (95% CI)
3rd NRRW	incidence	1955–2001	234	0.025 Sv (>0, 0.1+)	Linear	1.78 (0.17, 4.36)
A-bomb LSS cohort† (males, 20<=age at exposure <60)	incidence	1950–2001	93	0.50 Gy (0, 3.16)	Linear	2.04 (0.33, 6.85)
Techa River cohort	incidence	1953–2005	70	0.3 Gy (0, 2.0)	Linear	4.9 (1.6, 14.3)
A-bomb LSS cohort‡	incidence	1950–2001	312	0.64 Gy (0, 4.54)	Linear	2.78 (1.84, 4.01)

† The analysis is restricted to men who were exposed to A-bomb radiation at age 20–60 with weighted bone marrow dose ≤4 Gy. The ERR coefficient describes the excess RR at 1 Gy at age 50 after exposure at age 25.

‡ This analysis is for the full LSS cohort excluding unknown dose. The ERR coefficient describes the excess RR at 1 Gy at age 60 after exposure at age 25.

exposure) attained age highlights that, while highest excess risks are seen shortly after exposure for those exposed as children, at any given attained age the excess risks are generally higher for those exposed later in life (Fig. 1c and e). In addition, the NIC group was used in this study to augment the information on the variation in baseline rates. When all leukemias (or subtypes) other than CLL/ATL were examined, the inclusion or exclusion of the NIC group did not substantially change the risk estimates.

Richardson *et al*. (*7*) recently considered an ERR model for the LSS leukemia mortality in which the temporal variation was described in terms of an age-at-exposure dependent log cubic spline in time since exposure. That model (AIC = 2,445.6) did not describe the leukemia incidence data as well as did our preferred ERR model (AIC = 2,431.9).

In the BEIR VII study (*36*) and some other recent work on the LSS leukemia mortality data (*7*), the age-at-exposure effect on the excess risks was not allowed to vary among people who were more than 30 years old at the time of exposure. Imposing this constraint on our models resulted in a markedly poorer fit (AIC = 2,438.4 for the constrained model versus 2,431.89 for our preferred leukemia other than CLL or ATL model).

A major focus of this report was on the leukemia other than CLL or ATL as a group, which includes data on several different types of leukemia. To the extent that the cell-type distribution of the cases in this group in the LSS resembles that of many non-Japanese populations, the LSS risk data for this group can be useful for prediction or comparison with the radiation-related risk of leukemia other than CLL in other irradiated populations. Carrying out such additional analyses, we found that the predicted ERRs in the LSS cohort are consistent and comparable to those estimated in the studies of the National Registry of Radiation Workers (*37*) and the Techa River Cohort (*38*). Table 14 gives the comparison of risk estimate of the LSS cohort based on a relevant subset to the aforementioned cohorts.

Another focus was to characterize the radiation-related risk for specific types of leukemia. Leukemias other than CLL or ATL as a group, as well as ERRs for AML, ALL and CML considered separately, declined over time for all age groups. The temporal patterns in the type-specific EAR estimates are more complicated. Our analyses suggested that AML excess rates may have increased slightly over time, especially among people exposed after about age 30, while the EARs for ALL and CML have decreased over time. Those declines have often been interpreted as suggesting that the leukemia excess rates among the exposed returned to baseline levels 10–20 years after exposure. However, the analyses in this paper indicated that this is not the case for AML and ALL, as there was evidence of persistent risks 30 to 50 years after exposure for each of these types.

Cell-type specific leukemia risks and especially how they are modified by age and time, may be more useful in considering possible biological mechanisms for radiation-associated leukemogenesis than from analyses of a heterogeneous group of several types of leukemia combined. Some striking contrasts were noted between the type-specific excess rates. First, while AML exhibited a nonlinear upward-curving dose response, there was no evidence against linearity for either ALL or CML. Also, as noted above, AML excess rates tended to increase with increasing attained age for those exposed as adults, while ALL and CML excess rates appeared to decrease over time. While the radiation-related risk of CML seemed to decline with both age at exposure and time since exposure, the ALL excess rates decreased with attained age, but did not vary with either age at exposure or time since exposure.

The data suggest that the radiation associated excess rates for AML follow a U-shaped pattern in age, with excess rates falling for the youngest cohort members (who had to have been exposed early in life) and then increasing with attained age regardless of age at exposure. Although the current preferred EAR model for AML is much more simple than the 1994 model that involved complex interactions between age at exposure and time since exposure, the variation in the fitted excess rates with age are quite similar as shown in Fig. 2e and f. The temporal patterns for the ALL and CML excess rates differ significantly from those seen for AML. In

particular, excess rates for both ALL and CML, which were considerably greater than those for AML in the period shortly after the bombings, have decreased markedly over time. Thus, as indicated in Table 12, ALL and CML cases were the most common radiation-associated types and account for about 75% of the excess cases during the first 5 years of follow-up, i.e., years 5–10 after radiation exposure. If radiation markedly increased leukemia risks prior to 1950, as seems especially likely for ALL and CML, then the proportion of the radiation-associated excess ALL and CML cases in the first decade after exposure is likely to be even more striking than that which was suggested by the available data.

As the cohort members have aged, AML has become the predominant radiation-associated leukemia, accounting for over 80% of excess leukemia cases during the last 15 years of follow-up. It has been suspected that leukemia may be induced by specific translocations caused by radiation. However, spontaneous translocations specific to ALL are much more frequent than AML cases bearing the translocations. In addition, radiation-induced DNA damage is essentially random in the genome. Based on these observations, Nakamura (*39*) recently speculated that the radiation-related ALL risk in a population is almost entirely attributable to a small number of predisposed individuals in whom translocation-carrying pre-ALL cells have accumulated. He suggested that the short latency period for radiation-related ALL risk at young ages may be due to the small number of events needed for the conversion of pre-ALL cells present in newborns to full malignancy. Although CML occurs primarily in the elderly, the temporal risk pattern for CML is similar to that of ALL. BCR/ABL fusions have been linked to the majority of CML cases, but are also common in the general population (*40*). It may be that a very few additional mutations are required to convert the translocation-bearing pre-leukemic cells to tumor cells. Nakamura suspected the possibility of two different mechanisms: one for young-onset AML, which is clonally expanded similar to ALL, and the other for non-translocation-type AML, which like solid cancers, predominates in middle- and older-aged individuals, requiring a multi-step leukemogenesis process. The temporal patterns that we find for these three leukemia subtypes are generally consistent with Nakamura's hypothesis.

A recent study of myelodysplastic syndrome (MDS) risks among Nagasaki survivors for the period from 1985–2004 (*41*) showed a significant excess risk of MDS with an ERR/Gy estimate of 4.3 (95% CI 1.6–9.5), which is about twice the AML ERR estimate for the post-1986 period. People with MDS are known to have a higher risk of developing AML. However, it is of interest to note that the ERR for MDS after 1985 is larger than that for AML and that the shape of the dose response is quadratic for AML, but approximately linear for MDS. Further data on MDS incidence among LSS Nagasaki survivors and among Hiroshima survivors would help to better understand the relationship between MDS and AML excess risks.

It is likely that some cases identified as AML in the early years would have been classified as MDS if they were diagnosed with modern criteria. However, we feel that such misclassification is unlikely to have much impact on the inferences about AML risk estimates in the LSS, since (1) AML cases prior to the mid-1980s identified as MDS in the FAB review (*18*) were not used in the current analyses, (2) misclassification is less likely in the more recent years since MDS was recognized as a distinct condition, and (3) the AML baseline risk model includes a birth cohort effect that reduces the impact of period-specific misclassification. Any misdiagnosis of MDS as AML cases is likely to be independent of dose in which case it would not affect the ERR estimate of AML risk, though it would tend to increase the EAR estimate.

Chronic lymphocytic leukemia is very rare in Japan. Due to the small number of CLL cases in the LSS, radiation effects on CLL have not been considered in previous LSS reports. Although there were only 12 eligible cases, four of which occurred among survivors with doses in excess of 0.2 Gy, a simple trend test suggested a statistically significant dose response. Our results are consistent with findings of some, though not all, studies in the literature. A recent case-control study of leukemia in Chernobyl clean-up workers in Ukraine (*29*) and another such study in Belarus, Russia and Baltic countries (*42*) have shown increased risk of both CLL and leukemia other than CLL associated with radiation exposure. Similarly, a significantly increased risk of CLL as well as non-CLL leukemia was associated with radon and/or gamma radiation exposures in uranium miners (*28*). Conversely, no evidence of radiation-associated increases in the risk of CLL were seen in various other studies including the 15-country nuclear worker study (*43*), the Techa River cohort (*38*), the Mayak worker cohort (*44*), or UK radiation workers (*37*). The suggestion of a radiation effect on CLL risks in the LSS should be interpreted with caution and generalization to other populations may be unwarranted. In most Western populations, CLL accounts for 20% or more of all leukemia cases and an even higher proportion of leukemias seen late in life, but accounts for only about 3% of the LSS cases. Clinical data suggest that Japanese CLLs are largely dormant and genetically and biologically different from nonsmoldering CLLs seen in Western populations.

The large proportion of ATL in Nagasaki is not surprising. As reported in a nationwide study on ATL in Japan, ATL is endemic in Nagasaki (*45*). In the Nagasaki LSS, 42 out of 66 leukemia incident cases (63.6%) were diagnosed with ATL. There is no evidence of a radiation effect for ATL among Nagasaki LSS subjects, which may be due to the unusually high HTLV-I infections in the region.

The evidence for radiation effects on the risks of the other types of hematopoietic malignancies considered was less

clear cut. While there is no evidence of a radiation effect or dose response for HL or MM, the finding of a significant radiation-associated increase in NHL risks for men with no evidence of a radiation effect for women is similar to what has been reported in earlier analyses of NHL incidence (*4*) and mortality in the LSS (*46*). In the recent mortality analysis, Richardson *et al*. (*46*) considered ERR models for NHL mortality among LSS men who were 15–64 years old at the time of exposure and found a significant association that was most prominent 35 or more years after exposure. This is quite different than what is seen for the incidence data in which the ERR declines markedly with age (and hence time since exposure) whether or not the analysis is restricted to working age males. In our view, at best the LSS incidence data provide rather weak support for an NHL dose response among men with no evidence to support the idea that the risks are increasing with attained age or time since exposure.

Some early reports on myeloma mortality and incidence in the LSS have shown a statistically significant dose response for MM. The reasons for the differences between the findings of the incidence analyses and these earlier analyses were discussed in (*4*). To understand the difference, we also carried out an analysis of MM mortality in the cohort used for the current study. There were 111 MM deaths during the follow-up period including 86 MM cases used in the incidence analyses, and another 19 cases that were not used in the incidence analyses because they were either second primaries (10 cases) or not resident in the catchment area at the time of diagnosis (9 cases). Four of the remaining 6 cases had been rejected by the registries, while the other 2 cases had reports of solid cancers (both reported as renal cell carcinoma) with no indication of MM or any other hematopoietic malignancies. There was no evidence of statistically significant increases in either the ERR ($P = 0.12$) or the EAR ($P = 0.3$) with dose. The ERR and EAR point estimates were similar to those given above for the incidence data. This difference is largely due to uncertainties about the diagnosis of a small number of high-dose cases for which MM reported as the cause of death was not confirmed by the in-depth hematological review conducted for the incidence study. Taken together, the data provide little, if any, evidence of a radiation effect on MM. Although some worker studies including the most recent analysis of UK National Registry for Radiation Workers (*37*) and a study based on records from the National Dose Registry of Canada (*47*) provide some suggestion of a dose response for MM, the dose-response trends seen in those studies were not statistically significant. Results for MM mortality using extended follow-up are discussed in the latest LSS mortality report (*48*).

Increases in leukemia risks were one of the earliest significant long-term health effects detected among the atomic bomb survivors. However, in view of the declining radiation-related risk over the years, it has been thought that the radiation-associated excess risks would disappear over time. The present analyses that included information on cases diagnosed 43–56 years after exposure have provided important new insights into the persistent nature of the leukemia risks. The data suggest that, while radiation-associated excess risks for ALL and CML among the exposed have essentially returned to baseline levels by the end of follow-up, AML risks have persisted with excess rates that appear to be increasing with attained age (albeit not as rapidly as the baseline rates). It seems likely that the excess AML risks will persist throughout lifetime for people exposed at any age. This is similar to the temporal pattern for solid cancers. Since 40% of the cohort including most of those exposed as children, were still alive at the end of follow-up in this study, with continued follow-up of the LSS and evolving analytical methods, we expect that further insights will be gained into radiation effects on the leukemia and other hematopoietic malignancies.

APPENDIX

The online appendix tables include a listing of the morphological codes for the subtype groups and detailed descriptions of the parameterizations and parameter estimates for the preferred baseline and excess rate (ERR and EAR) models along with tables that describe (1) the impact of migration adjustment on person years (by city, gender, birth cohort and time period), (2) crude rates (by birth cohort, time period and dose category) and (3) alternative models for leukemia other than CLL or ATL, AML, ALL and CML (http://dx.doi.org/10.1667/RR2892.1.S3).

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