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Cancer Incidence in Atomic Bomb Survivors. Part Ill: Leukemia, Lymphoma and Multiple Myeloma, 1950–1987

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This paper presents an analysis of data on the incidence of leukemia, lymphoma and myeloma in the Life Span Study cohort of atomic bomb survivors during the period from late 1950 through the end of 1987 (93,696 survivors accounting for 2,778,000 person-years). These analyses add 9 additional years of follow-up for leukemia and 12 for myeloma to that in the last comprehensive reports on these diseases. This is the first analysis of the lymphoma incidence data in the cohort. Using both the Leukemia Registry and the Hiroshima and Nagasaki tumor registries, a total of 290 leukemia, 229 lymphoma and 73 myeloma cases were identified. The primary analyses were restricted to first primary tumors diagnosed among residents of the cities or surrounding areas with Dosimetry System 1986 dose estimates between 0 and 4 Gy kerma (231 leukemias, 208 lymphomas and 62 myelomas). Analyses focused on time-dependent models for the excess absolute risk. Separate analyses were carried out for acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelocytic leukemia (CML) and adult T-cell leukemia (ATL). There were few cases of chronic lymphocytic leukemia in this population. There was strong evidence of radiation-induced risks for all subtypes except ATL, and there were significant subtype differences with respect to the effects of age at exposure and sex and in the temporal pattern of risk. The AML dose–response function was nonlinear, whereas there was no evidence against linearity for the other subtypes. When averaged over the follow-up period, the excess absolute risk (EAR) estimates (in cases per 10^4 PY Sv) for the leukemia subtypes were 0.6, 1.1 and 0.9 for ALL, AML and CML, respectively. The corresponding estimated average excess relative risks at 1 Sv are 9.1, 3.3 and 6.2, respectively. There was some evidence of an increased risk of lymphoma in males (EAR = 0.6 cases per 10^4 PY Sv) but no evidence of any excess in females. There was no evidence of an excess risk for multiple myeloma in our standard analyses.

INTRODUCTION

By the late 1940s there were suggestions of an increased risk of leukemia among the survivors of the atomic bombings of Hiroshima and Nagasaki. These early observations led to the establishment of a registry of cases of leukemia and related disorders, including lymphomas, among atomic bomb survivors *(1).* In 1952 Folley *et al. (2)* reported clear evidence of an excess risk of leukemia, making this disease one of the first long-term health effects to be noted in this population. The Leukemia Registry data have been the basis of a series of reports *(3–5)* that have helped to clarify our understanding of the risks of radiation-induced leukemia. Since their establishment in 1958, the Hiroshima and Nagasaki tumor registries have also collected information on hematopoietic and lymphatic malignancies in these cities.

The most recent comprehensive reports on leukemia risks in the atomic bomb survivor population appeared more than 10 years ago. These reports considered the nature of the dose response *(6),* general patterns of leukemia incidence in the Life Span Study (LSS[1]) cohort from 1950 through 1978 *(7),* the distribution of onset times for leukemia cases reported to the Leukemia Registry between 1946 and 1975 *(8),* and

[1]Abbreviations used: AHS, Adult Health Study; ALL, acute lymphocytic leukemia; AMFIT, Additive Multiplicative Fitting Program for analysis of data for cohort survival from *Epicure User's Guide* (see ref. *26);* AML, acute myelogenous leukemia; ATB, at time of bombings; ATL, adult T-cell leukemia; DATAB, computer program from *Epicure User's Guide* (see ref. *26);* DS86, Dosimetry System 86; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; EAR, excess absolute risk; ERR, excess relative risk; HTLV, virus known to cause adult T-cell leukemia; FAB, French–American–British classification; ICD-O, International Classification of Diseases—Oncology; LSS, Life Span Study; NHL, non-Hodgkin's leukemia; NIC, not in city; RERF, Radiation Effects Research Foundation; T65D, tentative 1965 dosimetry; T65DR, tentative 1965 dosimetry revised.

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leukemia incidence among *in utero* survivors during the period 1945 through 1979 *(9).* Since the publication of these reports, leukemia incidence or mortality has been considered in several general LSS publications *(10–14).*

In the mid-1980s over 60% of the cases in the Leukemia Registry were reclassified using modern diagnostic criteria and nomenclature, including the French–American–British (FAB) classification *(15, 16).* Recently, Tomonaga *et al. (17)* analyzed the leukemia subtype data using all (LSS and non-LSS) reclassified cases for the period from 1945 through 1980. They suggest that relative risks for acute lymphocytic leukemia (ALL) and chronic myelocytic leukemia (CML) are greater than those for acute myelogenous leukemia (AML) and that there is no evidence of an excess risk for adult T-cell leukemia (ATL) or chronic lymphocytic leukemia (CLL).

Analyses of the A-bomb survivor population suggest that the risk of radiation-induced leukemia rises rapidly after exposure and then declines. In general, the initial peak in the excess (absolute or relative) risk is greater, and the decrease in the risk with time is more rapid, for those exposed when younger; indeed, for survivors who were over age 40 years at exposure, the decrease in the excess risk with time appears to be small or even nonexistent *(10).* Although leukemia is a rare disease, accounting for only 4% of the cancer deaths in the LSS, leukemias are estimated to have accounted for more than 20% of the excess cancer deaths in this cohort between 1950 and 1985.

Over the years there has also been an ongoing interest in the risks of lymphoma and multiple myeloma. Early analyses *(18)* of autopsy data suggest an increased prevalence of multiple myeloma, lymphosarcoma and Hodgkin's disease among survivors exposed within 1400 m of the hypocenter. Since then, Nishiyama *et al. (19)* noted an increased prevalence of lymphoma and multiple myeloma between 1945 and 1965 among survivors with Tentative 1965 Dosimetry System (T65D) dose estimates over 1 Gy. Ichimaru *et al. (5)* concluded that between 1950 and 1976 there was a statistically significant increase in the incidence of multiple myeloma among survivors with T65D dose estimates over 1 Gy that became apparent about 20 years after exposure. Both lymphoma and multiple myeloma are studied routinely as a part of the LSS mortality data. From 1950 through 1985 *(14)* 110 deaths were coded as malignant lymphoma and 36 as multiple myeloma. There was no evidence of an excess risk of lymphoma, but the estimated excess relative risk (ERR) for multiple myeloma was statistically significant. Indeed, the point estimate of this ERR is the largest for any of the cancers studied other than leukemia.

This report presents comprehensive data on incidence of leukemias, lymphomas (including Hodgkin's and non-Hodgkin's) and multiple myelomas occurring among members of the LSS cohort during the period from 1 October 1950, the date from which the LSS cohort was defined, through 31 December 1987. Unlike the companion paper on solid tumor incidence *(20),* which is based solely on data from the Hiroshima and Nagasaki tumor registries, the present analyses also include cases ascertained by the Leukemia Registry. As was the case with the data for solid tumor incidence, analyses were limited to first primary cancers diagnosed in the catchment areas of the Hiroshima and Nagasaki tumor registries.

MATERIALS AND METHODS

Study Population

These analyses are based upon a portion of the extended Life Span Study (LSS-E85) cohort of A-bomb survivors in Hiroshima and Nagasaki. As currently defined, the cohort includes 120,321 people, of whom 93,741 were in either city at the time of the bombings (ATB). Additional details about the LSS cohort and its extensions are given elsewhere *(11, 20).* In this study, as in most recent analyses of the LSS data, the 26,580 LSS members who were not in either city (NIC) ATB and 45 survivors for whom information on vital status was unobtainable were excluded from all analyses. Thus the basic data set includes 93,696 survivors. Except where explicitly noted, data for 7103 survivors for whom Dosimetry System 1986 (DS86) doses were not available and 262 survivors with DS86 doses greater than 4 Gy were excluded. An additional 38 people with cancer diagnoses prior to 1 October 1950 were also excluded. Thus the main analyses were based on the 86,293 LSS cohort members with DS86 kerma estimates less than 4 Gy.

Figure 1 summarizes the composition of the cohort used for this study by age at exposure, sex and vital status at the end of follow-up on 31 December 1987. As suggested by the data in this figure, the cohort included a relatively high proportion of women (58.4%) due to the relatively small number of males between the ages of 15 and 50 years in Hiroshima and Nagasaki ATB. Roughly two-thirds of the survivors in the LSS were in Hiroshima at the time of exposure. The average age at exposure of Nagasaki survivors is slightly less than that of Hiroshima survivors.

As noted above, a special Leukemia Registry was developed in the late 1940s and early 1950s *(1).* The Leukemia Registry includes data on cases of leukemia, lymphoma, multiple myeloma and related hematopoietic disorders diagnosed after 1945 among all survivors resident in Hiroshima and Nagasaki and surrounding areas, whether or not they are included in the LSS cohort. All cases of leukemia and multiple myeloma accepted by the Leukemia Registry are confirmed and classified by two or more experienced Leukemia Registry hematologists on the basis of relevant clinical records and histological materials. In the past, Leukemia Registry diagnoses were made using the nomenclature prevailing at the time of diagnosis and coded according to an *ad hoc* classification system. During the latter part of the 1980s, most Leukemia Registry leukemias were reclassified *(15–17)* using modern diagnostic criteria and disease classification systems, including the FAB system for acute leukemias *(21).* The reclassification also allowed identification of recently recognized disease entities, such as myelodysplastic syndrome and ATL. Sufficient material was available to reclassify about 60% of the Leukemia Registry leukemia cases. However, no additional efforts were made to reclassify Leukemia Registry cases for which diagnostic peripheral blood or bone marrow slides were inadequate or could not be located. The reclassified diagnoses will be called Leukemia Registry–FAB diagnoses.

Since 1957 in Nagasaki and 1958 in Hiroshima the tumor registries have been collecting cancer incidence data in the two cities. Details on tumor registry procedures and data quality are contained in papers by Mabuchi *et al. (22)* and Thompson *et al. (20).*

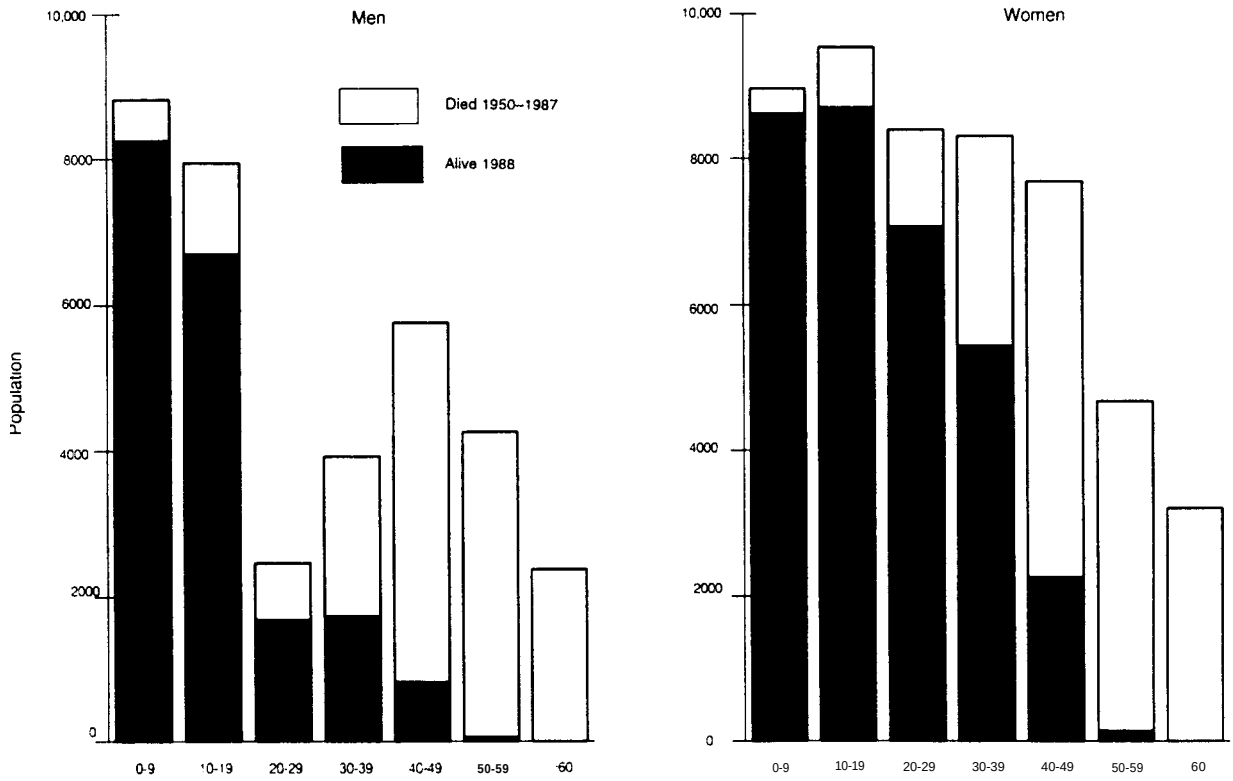

FIG. 1. LSS population by age at exposure, sex and vital status.

A detailed review and a comparison of the data on LSS cases from the various registries were carried out to identify potential cases. Appendix 1 contains a description of this review. Cases were classified in terms of International Classification of Disease—Oncology (ICD-O) morphology codes *(23).* The leukemia cases used here have ICD-O morphology codes in the range 980 to 994 augmented with adult T-cell leukemias (ICD-O morphology code 9702-3). Lymphoma cases have ICD-O morphology codes associated with Hodgkin's and non-Hodgkin's lymphomas (959–963, 969) or reticulosarcoma (964). Multiple myeloma cases have a three-digit ICD-O morphology code of 973.

A total of 339 leukcmias, 304 lymphomas and 94 myelomas occurred among members of the LSS. Analyses were limited to cases among exposed members of the LSS diagnosed between October 1, 1950 and the end of 1987. Following the procedures developed for the report on the incidence of solid tumors *(20),* the primary analyses were limited to initial primary cancers diagnosed among residents of the two cities. Table I presents summary information on the final diagnoses classified by subtype. Most analyses were based on the 481 cases with DS86 kerma estimates of 4 Gy or less.

Dosimetry

The latest version of the DS86 *(24, 25)* was used for these analyses. This version of DS86 provides dose estimates for 92% of the survivors in the LSS-E85 cohort. Although the basic tabulations (described below) were made in terms of total bone marrow dose in grays, DS86 weighted bone marrow doses in sieverts were computed as the sum of the DS86 γ–ray dose to the bone marrow and ten times the DS86 neutron dose to the bone marrow. This is equivalent to the assumption of a constant relative biological effectiveness (RBE) of ten for neutrons. Weighted doses were used for all analyses. Occasionally, risks for exposed and comparison groups are compared. The comparison group includes all survivors in the LSS-E85 cohort with total bone marrow doses below 0.01 Gy.

Statistical Analysis

Person-year computation. As in the companion report on solid tumor incidence *(20),* analyses were based on a detailed tabulation of case counts and person-years stratified by age at exposure (13 categories). DS86 bone marrow dose (11 categories, including a dose-unknown category), calendar time (10 categories), sex and city. The cutpoints for age at exposure were 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 years. The cutpoints for the bone marrow dose (in Gy) are 0.01, 0.10, 0.20, 0.50, 1.00, 1.50, 2.00, 3.00 and 4.00, with a category for survivors without DS86 estimates. Follow-up continued from 1 October 1950 until the earliest of (a) the date of diagnosis of the first primary cancer (including *in situ* and occult cancer), (b) the date of death or (c) 31 December 1987. The calendar time cutpoints were 1 January 1953, 1955, 1958, 1961, 1966, 1971, 1976, 1981 and 1986.

The tables contain a row for each combination of the stratification variables in which at least one person is at risk. In addition to case counts and person-year totals, each row in these tables includes person-year-weighted averages of age at exposure, attained age, time since exposure and bone marrow dose (γ rays, neutrons and total). These tables were made using DATAB *(26).*

There were a total of 2,778,000 PY among exposed members of the LSS-E85 cohort. This total includes 2,554,000 PY for the survivors with DS86 bone marrow doses between 0 and 4 Gy, 216,000 PY accumulated by people for whom DS86 estimates are not available, and 7000 PY for survivors with DS86 kerma estimates over 4 Gy.

Migration adjustment. An adjustment for the effects of migration on the completeness of ascertainment similar to that used in the companion report on solid tumor incidence *(20)* was made using methods described by Sposto and Preston *(27).* Cases diagnosed outside the tumor registry catchment areas were excluded and person-years were scaled using city-sex-, age- and time-specific weights based upon an analysis of migration rates in the Radiation Effects Research Foundation (RERF) Adult Health Study (AHS) cohort for the period 1958 through 1987. Because

TABLE I
Leukemia, Lymphoma in Myeloma in the LSS. Summary of Final Diagnosis

	Eligible for analysis				Exclusions				
	0-4 Gy	>4 Gy	Unknown dose	Total	Nonresident	Second primary	<1950 or >1987	NIC	Total
Leukemia	231	6	24	261	21	8	17	32	339
ALL	*32*	*2*	*4*	*38*	*6*	*1*	*2*	*4*	*51*
AML	*103*	*2*	*12*	*117*	*8*	*3*	*6*	*18*	*152*
CML	*57*	*2*	*3*	*62*	*4*	*2*	*9*	*2*	*79*
Other	*39*	*0*	*5*	*44*	*3*	*2*	*0*	*8*	*57*
Lymphoma	191	0	19	210	12	7	10	65	304
Non-Hodgkin's	*170*	*0*	*18*	*188*	*8*	*6*	*10*	*55*	*267*
Hodgkin's	*21*	*0*	*1*	*22*	*4*	*1*	*0*	*10*	*37*
Myeloma	59	1	5	65	2	6	1	20	94
Total	481	7	48	536	35	21	28	117	737

[a]Summarizes the final diagnoses for all cases accepted during the review. The main analyses were base on the 481 first-primary cases in the left-most column of the table. Survivors with Dosimetry System 1986 (DS86) kerma greater than 4 Gy or unknown were used in analyses of effect modification. Cases diagnosed among persons who were not resident in the cities (NIC) at the time of diagnosis were excluded as were all second primary cases among members of the Life Span Study (LSS) and cases with diagnosis dates outside the follow-up period for the present study.

follow-up for this study began in 1950, a slight modification to the person-year adjustment procedure was necessary. This was done by linear extrapolation of the catchment-area residency probabilities from a value of one on 1 October 1950 to the 1958 fitted values estimated from the AHS.

After the residency adjustment, the numbers of leukemia, lymphoma and multiple myeloma cases were reduced by 21, 12 and 2, respectively (Table I). The number of person-years for survivors with DS86 kerma estimates between 0 and 4 Gy was reduced 12% to 2,243,000. Table II provides a summary of the effects of the person-year adjustment by city, sex and age at exposure. There has been a substantial amount of migration among the youngest survivors, especially in Nagasaki.

Statistical Methods

Modeling methods based on Poisson regression were used to study the variation in risk as a function of weighted dose *(d),* sex *(s),* city *(c),* attained age *(a),* birth cohort *(b),* age at exposure *(g)* and time since exposure *(t).*

Two classes of models were considered: (1) ERR models of the form

$$\lambda(c,s,a,b)\,[1 + \rho(d)\,\varepsilon_1(c,s,g,t,a)\,],$$

where $\lambda(\cdot)$ is a model for the background rate, i.e., the incidence function among people with zero dose, $\rho(d)$ is a dose–response function, and $\varepsilon_1(\cdot)$ describes effect modification; and (2) excess absolute risk (EAR) models of the form

$$\lambda(c,s,a,b) + \rho(d)\,\varepsilon_2(c,s,g,t,a).$$

Recently, radiation effects on cancer morbidity have usually been described in terms of time-constant ERR models. In the companion paper on solid tumor incidence in the LSS *(20)* we have taken that approach. However, in these analyses EAR models are emphasized because (1) the time-dependent ERR models needed to model the risk of radiation-induced leukemias are just as complex as the EAR models, and (2) presentation of the results in terms of excess cases and time-dependent excess rates provides a clearer picture of the risks, especially for younger survivors in the early years of follow-up, when the ERR estimates for leukemia can be extremely large.

Background rates, i.e., the rates one would expect in this population in the absence of exposure, were modeled as functions of city, sex, attained age and birth cohort. Birth cohort was included to allow for secular trends in the background rates. Because of the relatively small number of cases for many of the malignancies considered here, we tried to find the most parsimonious model for each disease. We started with a model in which the log rates among survivors with doses less than 0.1 Gy were described as log-quadratic functions of attained age. We then examined sex, city and cohort effects, choosing parameters with statistically significant ($P < 0.05$) effects for inclusion in the final model. After developing a model for the radiation effect, we re-examined the background rate model.

We routinely considered linear, linear–quadratic and linear-spline models for the dose–response function. The linear–quadratic dose–response function can be written as

$$\rho(d) = \gamma_1 d + \gamma_2 d^2,$$

whereas the linear-spline model is

$$\rho(d) = \begin{cases} \gamma_1 d & \text{if } d < c \\ (\gamma_1 + \gamma_2)d - \gamma_2 c & \text{if } d >= c. \end{cases}$$

When γ_1 is fixed at 0 this model becomes a linear-threshold model with a threshold at dose *c.* We fixed *c* at 0.5 Gy and did not attempt to find a "best" estimate for the threshold.

Log-linear functions, i.e., $\varepsilon(z) = e^{\beta z}$, were used to describe effect modification. When looking at temporal effects on the excess risk, both *t* and log *(t)* were considered. When *t* is used as a covariate in ε the temporal trend will be called a log-linear model since $\log(e^{\beta t}) = \beta t$, whereas when log *(t)* is used the model will be called a power function since $e^{\beta \log(t)} = t^{\beta}$.

Analyses of the LSS data commonly have excluded data on survivors for whom dose estimates are unavailable. However, the data for these individuals can be used in inference about effect modification under the assumptions that: (1) among persons with unknown dose the distribution of the true (but unknown) dose is independent of the covariates in *z,* and (2) we can classify people with unknown dose as exposed or unexposed. In this report we occasionally have used models in which the effect-modification term is multiplied by a dose–response function of the form

$$\rho(d) = \begin{cases} (\gamma_1 d + \gamma_2 d^2 & \text{known DS86} \\ \gamma_3 & \text{unknown DS86.} \end{cases}$$

Analyses based on this extended model were used only to supplement the standard analyses. Results based on these models are reported when they modify or clarify the findings of the standard analyses.

Parameter estimates were computed using maximum-likelihood methods for grouped survival data (Poisson regression). Hypothesis tests were based on likelihood-ratio tests. However, when implicit restrictions on the parameter space precluded computation of the likelihood-ratio

TABLE II
Person-years and Adjusted-person-year Distribution by Sex, City and Age ATB

		Hiroshima		Nagasaki		
Age ATB (years)		Males	Females	Males	Females	Both cities, both sexes
0-19	PY	367,414	413,955	227,334	251,574	1,260,277
	Adjusted PY	305,692	355,671	163,141	190,414	1,014,918
	Percentage change	16.8%	14.1%	28.2%	24.3%	19.5%
20–39	PY	141,359	394,855	53,172	159,605	748,991
	Adjusted PY	134,902	377,105	48,675	146,125	706,807
	Percentage change	4.6%	4.5%	8.5%	8.4%	5.6%
>=40	PY	158,022	237,973	59,286	89,731	545,012
	Adjusted PY	151,758	229,792	55,230	84,418	521,197
	Percentage change	4.0%	3.4%	6.8%	5.9%	4.4%

statistic, score tests were used. Ninety-five percent confidence intervals (95% CI) were computed from the profile likelihood function *(28)*. Parameter estimation and testing were carried out using AMFIT *(26)*.

The Results section contains short, nonmathematical descriptions of the final models, supplemented by plots of the risk functions for selected covariate values. Because it is not possible to show data points on such plots, approximate 95% confidence bands are used to illustrate the uncertainty in these fits. These hands were obtained from pointwise profile likelihood bounds. Tables of the estimated number of background and excess cases are also provided for most analyses. These estimates are sums of cell-specific values computed from the final risk model for the outcome of interest. The final model for each type of malignancy considered is presented in Appendix 2. For an EAR model of the form $\lambda(\cdot) + \rho(d)\varepsilon_A(\cdot)$, the estimated numbers of background and excess cases in a cell with P_i person-years at risk are $P_i\lambda(\cdot)$ and $P_i\rho(d)\varepsilon_A(\cdot)$, respectively. Model-based, time-averaged summary estimates of the $ERR_{1\ Sv}$, EAR and the attributable risk (AR) among survivors with doses over 0.01 Gy ($AR_{0.01\ Gy}$) are derived from the values in these tables. The computation of this ERR estimate uses the mean weighted dose and, for nonlinear dose–response models, the mean of the squared weighted dose for surivors in the expected (bone marrow dose greater than 0.01 Gy) group. These values are 0.26 Sv and 0.29 Sv^2, respectively. The total number of person-year sieverts (after adjustment for migration) in the cohort to date is 273,860, the value used in the computation of the summary EAR estimate.

RESULTS

Table III presents a summary of the case counts, crude rates, person-years and mean weighted dose values for the three major classes of malignancies considered for this report. The data are classified by age at exposure, period and dose category. Table IV provides a similar summary of the case counts and crude rates for the leukemia subtypes considered in these analyses. Many of the patterns described on the basis of the models considered below can be seen in these data. For example, the leukemia rates suggest a strong dose response, the magnitude of which depends on time and age at exposure.

Leukemia: All Types

As shown in Table I, 261 leukemia cases met the basic criteria for use in these analyses. Among these cases, 231 had DS86 kerma estimates between 0 and 4 Gy and 6 had estimated kerma over 4 Gy; for 24 cases DS86 estimates could not be computed.

Expected rates in the absence of exposure (background rates). The background rates for all types of leukemia combined can be described by a model in which the log of the rate is a quadratic function of the log of attained age. The age-specific rates for women are about half of those seen in men, but the rate of increase with age does not appear to depend on sex. There is a significant secular trend with age-specific rates increasing by 2.2% for each year increase in the year of birth. The data do not suggest a city difference in the background rates when all types are combined. Parameter estimates for the leukemia background rates and excess risks are presented together with those for other tumor types in Appendix 2. Figure 2 contains plots of the fitted background rate as a function of age for men and women in several birth cohorts.

Excess risks. There is a statistically significant dose response ($P < 0.001$) that appears to be nonlinear in dose ($P = 0.008$). As indicated in Fig. 3, the dose response is concave upward. Although the linear–quadratic and spline models provided comparable fits for these data, the hypothesis of a 0.5-Sv threshold could be rejected ($P < 0.001$). The EAR was best described by a time-dependent model in which the temporal pattern depends on both age at exposure and sex. If the effects of age at exposure and sex were ignored, the EAR was seen to decrease significantly with time ($P < 0.001$) at a rate of about 6.5% per year. After allowance is made for this temporal trend, there is no evidence for an independent effect of age at exposure ($P = 0.5$); however, the addition of both an effect of age at exposure and an interaction between age at exposure and time, in which risks for those exposed earlier in life decreased more rapidly than did risks for older survivors, improved the fit significantly ($P = 0.02$, 2 df). Similarly, sex alone did not appear to have an effect ($P = 0.08$), whereas the addition of an interaction between sex and time did lead to a better fit ($P = 0.01$, 2 df). With this model, risks for women decreased less rapidly with time than did those for men. The effects of sex and age at exposure were largely independent. The EAR did not depend on city ($P > 0.5$). Inclusion of survivors with unknown dose did not change the results significantly.

TABLE III
LSS Leukemia, Lymphoma and Myeloma Data Case Counts and Crude Rates[a]

Type	Age at exposure (year)	Dose (Gy)	1950–1952 <0.01	1950–1952 0.01–0.99	1950–1952 >=1	1953–1957 <0.01	1953–1957 0.01–0.99	1953–1957 >=1	1958–1969 <0.01	1958–1969 0.01–0.99	1958–1969 >=1	1970–1987 <0.01	1970–1987 0.01–0.99	1970–1987 >=1	Total >=0.01	Total 0.01–0.99	Total >1
Leukemia	0–19		1	4	3	4	6	5	6	9	5	11	11	3	22	30	16
			(0.3)	(1.3)	(15.4)	(0.5)	(0.9)	(12.0)	(0.3)	(0.6)	(5.1)	(0.5)	(0.6)	(2.7)	(4)	(0.7)	(5.9)
	20–39		2	1	3	1	2	3	7	8	4	22	22	3	32	33	13
			(0.8)	(0.4)	(21.8)	(0.2)	(0.4)	(9.9)	(0.5)	(0.7)	(5.6)	(1.5)	(1.6)	(4.1)	(0.9)	(1.0)	(6.8)
	≥40		2	5	2	4	7	2	12	14	7	18	8	4	36	34	15
			(0.6)	(1.8)	(15.6)	(0.6)	(1.3)	(7.7)	(1.1)	(1.4)	(14.3)	(2.9)	(1.4)	(16.1)	(1.3)	(1.4)	(13.3)
Lymphoma	0–19		0	0	0	0	3	0	9	1	1	11	12	0	20	16	1
			(0)	(0)	(0)	(0)	(0.5)	(0)	(0.5)	(0.1)	(1.0)	(0.5)	(0.6)	(0)	(0.4)	(0.4)	(0.4)
	20–39		3	0	0	2	1	0	10	9	1	25	23	2	40	33	3
			(1.2)	(0)	(0)	(0.4)	(0.2)	(0)	(0.7)	(0.7)	(1.4)	(1.7)	(1.7)	(2.7)	(1.1)	(1.0)	(1.6)
	≥40		1	0	0	6	5	0	17	15	2	1	10	1	44	30	3
			(0.3)	(0)	(0)	(1.0)	(0.9)	(0)	(0.9)	(1.5)	(4.1)	(3.4)	(1.8)	(4.0)	(1.6)	(1.2)	(2.7)
Melanoma	0–19		0	0	0	0	0	0	0	0	0	2	3	0	2	3	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0.1)	(0.2)	(0)	(0.0)	(0.1)	(0)
	20–39		0	0	0	0	1	0	1	1	1	9	6	0	10	8	1
			(0)	(0)	(0)	(0)	(0.2)	(0)	(0.1)	(0.1)	(1.4)	(0.6)	(0.4)	(0)	(0.3)	(0.2)	(0.5)
	≥40		0	0	0	0	0	0	1	5	0	15	11	0	16	16	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0.1)	(0.5)	(0)	(2.4)	(2.0)	(0)	(0.6)	(0.7)	(0)
Person years	0–19		38,126	31,534	1,954	79,380	66,225	4,151	190,869	160,494	9,835	228,457	192,586	11,306	536,832	450,839	27,246
	20–39		24,786	22,626	1,379	54,903	50,036	3,035	133,342	121,617	7,178	146,959	133,553	7,393	359,991	327,832	18,985
	≥40		30,893	27,309	1,286	61,659	54,966	2,595	114,222	102,094	4,882	62,517	56,291	2,484	269,291	240,661	11,247
Weighted dose (Sv)	0–19		0.00	0.16	1.83	0.00	0.16	1.82	0.00	0.16	1.82	0.00	0.16	1.82	0.00	0.16	1.82
	20–39		0.00	0.17	1.77	0.00	0.17	1.78	0.00	0.17	1.77	0.00	0.17	1.75	0.00	0.17	1.76
	>=40		0.00	0.17	1.76	0.00	0.17	1.75	0.00	0.17	1.74	0.00	0.17	1.71	0.00	0.17	1.74

[a] Cases are classified by age at exposure, time, and DS86 bone-marrow dose. Rates per 10,000 PY are shown in parentheses. Summary information on migration-adjusted PY and average DS86 weighted bone marrow dose is also shown.

As can be seen in Fig. 4, young men had high EARs in the period from 5 to 10 years after exposure, but these risks have decreased rapidly with time. The EARs for older men are not as high in the early years and decline more slowly than those for younger men. Women tended to have lower excess risks than men until roughly 20 years after exposure. The data for older women suggest that the risks have not decreased with time.

TABLE IV
LSS Leukemia Subtype Data Case Counts and Crude Rates[a]

Type	Age at exposure (year)	Dose (Gy)	1950–1952 <0.01	1950–1952 0.01–0.99	1950–1952 >1	1953–1957 <0.01	1953–1957 0.01–0.99	1953–1957 >=1	1958–1969 <0.01	1958–1969 0.01–0.99	1958–1969 >=1	1970–1987 <0.01	1970–1987 0.01–0.99	1970–1987 >=1	Total <0.01	Total 0.01–0.99	Total ≥1
ALL	0–19		0	2	3	0	2	2	2	3	2	1	2	0	3	9	7
			(0)	(0.6)	(15.4)	(0)	(0.3)	(4.8)	(0.1)	(0.2)	(2.0)	(0.0)	(0.1)	(0)	(0.1)	(0.2)	(2.6)
	20–39		0	0	0	0	0	0	1	0	1	2	1	1	3	1	2
			(0)	(0)	(0)	(0)	(0)	(0)	(0.1)	(0)	(1.4)	(0.1)	(0.1)	(1.4)	(0.1)	(0.0)	(1.1)
	≥40		0	0	0	0	1	1	2	2	0	1	0	0	3	3	1
			(0)	(0)	(0)	(0)	(0.2)	(3.9)	(0.2)	(0.2)	(0)	(0.2)	(0)	(0)	(0.1)	(0.1)	(0.9)
AML	0–19		0	2	0	2	1	1	2	4	2	6	6	2	10	13	5
			(0)	(0.6)	(0)	(0.3)	(0.2)	(2.4)	(0.1)	(0.2)	(2.0)	(0.3)	(0.3)	(1.8)	(0.2)	(0.3)	(1.8)
	20–39		0	0	0	1	1	1	2	4	1	11	11	1	14	16	3
			(0)	(0)	(0)	(0.2)	(0.2)	(3.3)	(0.1)	(0.3)	(1.4)	(0.7)	(0.8)	(1.4)	(0.4)	(0.5)	(1.6)
	≥40		1	0	2	3	2	0	4	5	6	11	5	3	19	12	11
			(0.3)	(0)	(15.6)	(0.5)	(0.4)	(0)	(0.4)	(0.5)	(12.3)	(1.8)	(0.9)	(12.1)	(0.7)	(0.5)	(9.8)
CML	0–19		0	0	0	1	2	2	2	2	1	1	2	1	4	6	4
			(0)	(0)	(0)	(0.1)	(0.3)	(4.8)	(0.1)	(0.1)	(1.0)	(0.0)	(0.1)	(0.9)	(0.1)	(0.1)	(1.5)
	20–39		0	1	3	0	1	2	2	3	0	5	3	1	7	8	5
			(0)	(0.4)	(21.8)	(0)	(0.2)	(6.6)	(0.1)	(0.2)	(0)	(0.3)	(0.2)	(1.4)	(0.2)	(0.2)	(3.2)
	≥40		0	4	0	0	4	0	2	4	1	4	2	1	6	14	2
			(0)	(1.5)	(0)	(0)	(0.7)	(0)	(0.2)	(0.4)	(2.0)	(0.6)	(0.4)	(4.0)	(0.2)	(0.6)	(1.8)
Other	0–19		1	0	0	1	1	0	0	0	0	3	1	0	5	2	0
			(0.3)	(0)	(0)	(0.1)	(0.2)	(0)	(0)	(0)	(0)	(0.1)	(0.1)	(0)	(0.1)	(0.0)	(0)
	20–39		2	0	0	0	0	0	2	1	2	4	2	0	8	8	2
			(0.8)	(0)	(0)	(0)	(0)	(0)	(0.1)	(0.1)	(2.8)	(0.3)	(0.5)	(0)	(0.2)	(0.2)	(2.1)
	≥40		1	1	0	1	0	1	4	3	0	2	1	0	8	5	1
			(0.3)	(0.4)	(0)	(0.2)	(0)	(3.9)	(0.4)	(0.3)	(0)	(0.3)	(0.2)	(0)	(0.3)	(0.2)	(0.9)

[a] Leukemia cases are classified by subtype, age at exposure, time and DS86 bone marrow dose category. Rates per 10,000 PY are shown in parentheses.

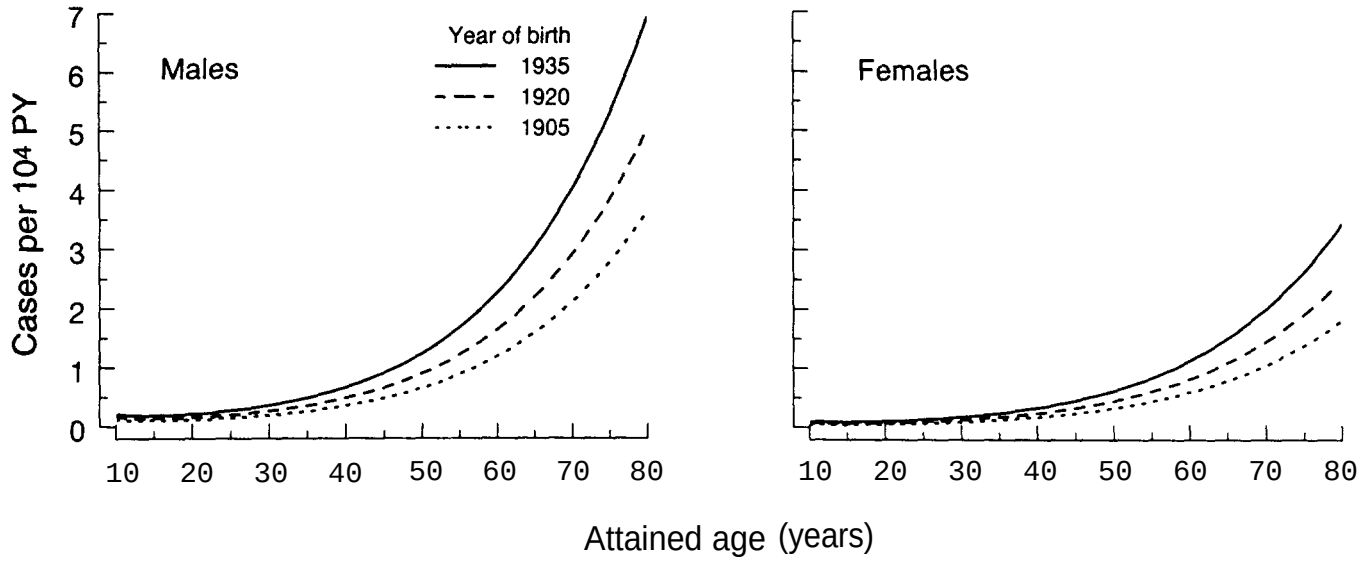

FIG. 2. Leukemia, all types—background rates. Fitted background rates for men and women in selected birth cohorts. The curves are based on the model given in Appendix 1.

Table V presents a summary of the observed and fitted numbers of leukemia cases by sex, age at exposure, period and exposure status derived from the final model developed for this report. If the data in Table V are used, a model-based estimate of the time-averaged $ERR_{1\ Sv}$ adjusted for the nonlinearity in the dose response is 3.9. Model-based estimates of the EAR and $AR_{0.01\ Gy}$ are 2.7 cases per 10^4 PY Sv and 50%, respectively. Despite the tendency for leukemia risks to decrease with time, these $ERR_{1\ Sv}$ and $AR_{0.01\ Gy}$ values are larger than the corresponding estimates for any of the solid tumors.

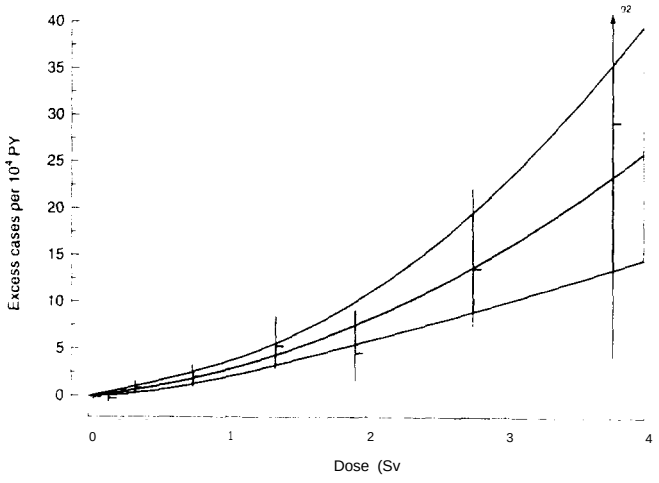

FIG. 3. The solid curve is the fitted leukemia dose response based on a quadratic excess absolute risk (EAR) model without effect modification. The shaded area is a 95% confidence region for the fitted curve. The vertical lines are 95% confidence intervals for dose-category-specific risks. Point estimates of the risk for each category are indicated by short horizontal lines.

Acute Lymphocytic Leukemia

Of the 38 ALL cases that met the basic criteria for inclusion in the study, 32 had DS86 kerma estimates between 0 and 4 Gy (Table I). Because of the small number of cases and the relatively high percentage of cases with unknown dose, the analyses of effect-modifying factors were supplemented by analyses that used survivors with unknown D86.

Background rates. Although the small number of ALL cases precluded precise estimation, patterns are described based on the limited data available. There was an increase in the ALL background rates that was roughly log-linear in attained age (Fig. 5) and was similar for males and females ($P > 0.5$). There was no indication that the age-specific rates changed with time ($P = 0.4$).

Excess risks. The test for a dose response was highly significant ($P < 0.001$), with a weak suggestion of upward curvature in both the quadratic ($P = 0.16$) and linear-spline ($P = 0.13$) models. There was no significant difference between the fit of the linear-spline and threshold models ($P > 0.5$). Analyses of effect modification described below are based on the linear model; virtually identical results were obtained for the quadratic model.

The EAR has decreased with time since exposure ($P < 0.001$) and the time-averaged EAR decreased with increasing age at exposure ($P = 0.01$). After allowing for the temporal trend, the evidence for an effect of age at exposure on the risk was increased ($P = 0.002$). When sex was considered as an effect modifier in the standard analyses, i.e., excluding survivors with unknown DS86 dose estimates or with estimates over 4 Gy, the EAR for women was estimated to be about 40% of that for men, but this difference was

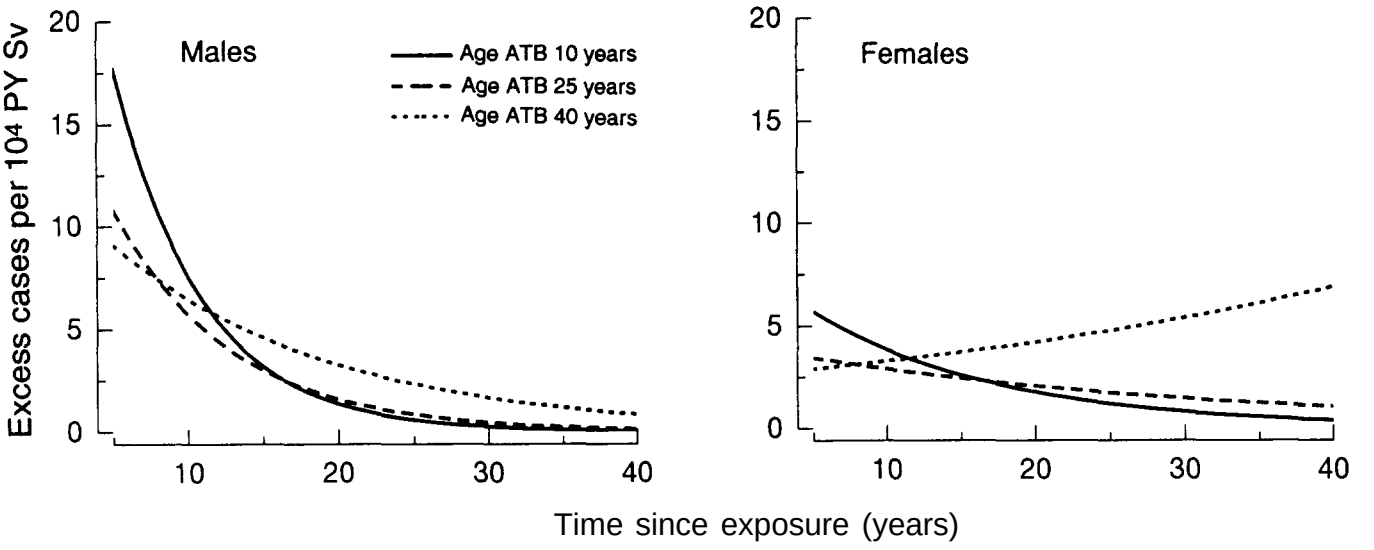

FIG. 4. Leukemia, all types—excess absolute risks. Fitted EAR estimates for survivors receiving 1-Sv bone marrow equivalent doses. Curves are shown for male and female survivors at selected ages at exposure. The curves are based on the model presented in Appendix 1.

not statistically significant (P = 0.09; 95% CI = 13–113%). However, when the effect-modification analyses were repeated with the addition of survivors with unknown doses, the sex difference was found to be statistically significant (P = 0.03, 95% CI = 12–91%). The EAR did not appear to differ between the two cities (P > 0.5).

Our final model for the ALL risk is a linear dose–response model in which the EAR has decreased rapidly with time, about l4% per year. Children exposed under age 10 had the highest excess risks. The EAR was estimated to decrease by about 5% for each year's increase in age at exposure. For any age at exposure or time since exposure, the EAR estimates for women were estimated to be less than half those for men. Figure 6 shows plots of the EAR for men and women exposed to 1 Sv at the ages of 10, 25 and 40 years. Confidence bands are shown only for males.

Over the current follow-up the standard summary estimate of the $ERR_{1\ Sv}$ for ALL is 10.3 (95% CI = 4.3–25). EAR and $AR_{0.01\ Gy}$ estimates derived from this value are 0.57 cases per 10^4 PY Sv (95% CI = 0.35–0.78) and 72% (95% CI = 51.5–86.5%), respectively. The observed and fitted values in Table VI provide a more detailed picture of these data. The model-based summary risk estimates derived from this table are $ERR_{1\ Sv}$ = 9.1, EAR = 0.62 per 10^4 PY Sv and $AR_{0.01\ Gy}$ = 70%.

Acute Myelogenous Leukemia

There were 103 eligible cases among survivors with DS86 estimates less than 4 Gy. In addition there were two cases whose DS86 dose estimates were greater than 4 Gy and 12 cases for whom DS86 estimates could not be computed (Table I).

Background rates. AML background rates in this cohort could be described by a model in which the log rate varied as a sex-dependent quadratic function of log attained age with an effect of birth cohort. The sex-dependent difference could not be described fully in terms of a simple ratio since the pattern of the increase in risk with attained age also differed by sex (P = 0.02, after allowing for a difference in the level of risk for men and women). Age-specific rates for women under the age of 40 were slightly higher than the corresponding rates for men, whereas this pattern was reversed at later ages (Fig. 7). Age-specific rates for both sexes increased by about 25% for each year increase in the year of birth (P = 0.01). There was no significant city difference (P = 0.13).

Excess risk. There was strong evidence of a dose response (P < 0.001) and a suggestion of nonlinearity, as indicated by tests based on either quadratic (P= 0.05) or spline models (P

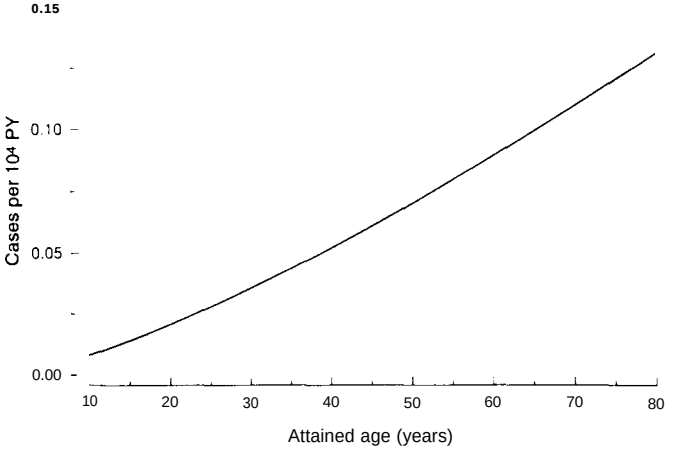

FIG. 5. Acute lymphocytic leukemia—background rates. The fitted background rate is based on the model given in Appendix 1. This model does not depend on sex, city or birth cohort.

TABLE V

Leukemia, All Types, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (years)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	3	19	9	8	12	27
	Fitted background	2.91	2.62	10.85	9.91	13.76	12.53
	Fitted excess	0.06	16.16	0.00	1.08	0.07	17.24
20–39	Cases	3	8	13	12	16	20
	Fitted background	2.68	2.49	8.52	7.98	11.21	10.47
	Fitted excess	0.02	5.98	0.00	0.74	0.02	6.72
>=40	Cases	8	17	11	7	19	24
	Fitted background	8.39	7.99	8.73	8.44	17.12	16.43
	Fitted excess	0.03	10.71	0.01	1.69	0.04	12.40
All ages	Cases	14	44	33	27	47	71
	Fitted background	13.99	13.1O	28.10	26.32	42.09	39.43
	Fitted excess	0.1 1	32.86	0.01	3.50	0.12	36.36
		Females					
0-19	Cases	4	11	6	8	10	19
	Fitted background	1.73	1.52	6.74	5.90	8.46	7.43
	Fitted excess	0.04	9.56	0.01	3.20	0.05	12.76
20–39	Cases	3	6	13	20	16	26
	Fitted background	3.24	3.19	12.34	11.96	15.58	15.15
	Fitted excess	0.03	7.68	0.02	5.03	0.05	12.72
>=40	Cases	5	13	12	12	17	25
	Fitted background	5.90	5.38	8.55	7.85	14.45	13.23
	Fitted excess	0.03	6.42	0.03	6.64	0.06	13.06
All ages	Cases	12	30	31	40	43	70
	Fitted background	10.87	10.09	27.62	25.71	38.49	35.81
	Fitted excess	0.10	23.66	0.07	14.88	0.16	38.54
		Both Sexes					
All ages	Cases	26	74	64	67	90	141
	Fitted background	24.85	23.20	55.73	52.04	80.58	75.24
	Fitted excess	0.21	56.52	0.08	18.38	0.29	74.90

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

= 0.04). After allowance was made for the effects of age at exposure, nonlinearity of the dose response became more apparent *(P* = 0.02). The 0.5-Gy threshold model did not fit the data as well as the spline model *(P* = 0.05). The AML dose–response function is contrasted with those for other leukemia subtypes in a later section.

Age at exposure had a significant effect on the EAR *(P* = 0.04), with the youngest survivors having the highest average absolute excess risks. Evaluation of other potential effect-modifying factors individually revealed no significant effects of time since exposure *(P* = 0.4), sex *(P* = 0.4) or city *(P* = 0.2). However, after allowing for the effect of age at exposure, the

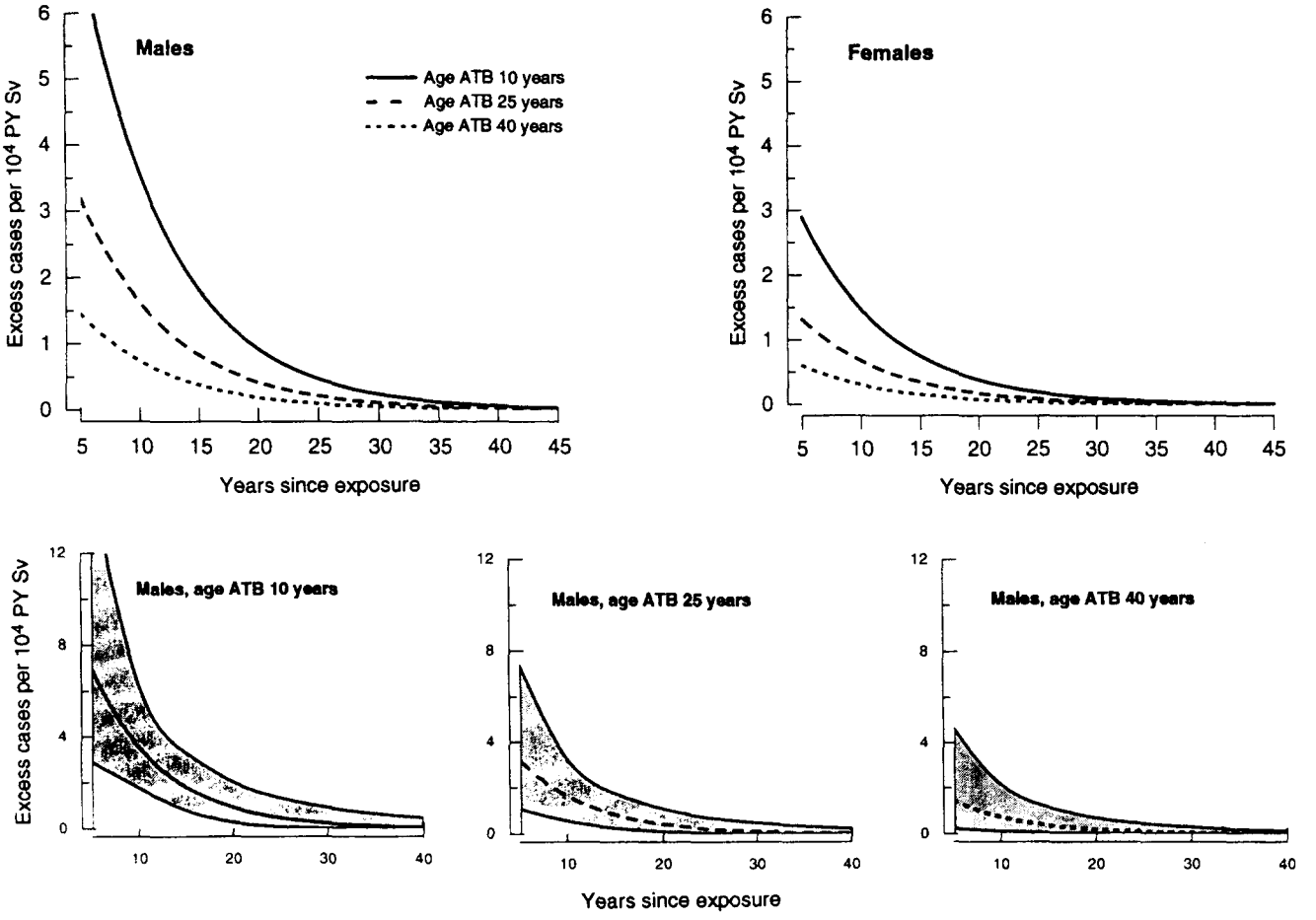

FIG. 6. Acute lymphocytic leukemia—excess absolute risks. Fitted EAR estimates for survivors receiving 1-Sv bone marrow equivalent doses. Curves are shown for male and female survivors at selected ages at exposure. The curves are based on the model presented in Appendix 1. The shaded areas in the lower panels indicate 95% confidence regions for the curves for males.

addition of both log time and an interaction between age at exposure and log time leads to a marginal improvement in the fit of the model (P = 0.15, 2 df). Inclusion of the data for survivors with unknown doses (14 cases and 186,300 PY) strengthened the evidence for temporal trends dependent on age at exposure in the EAR (P = 0.005, 2 df). To reduce the likelihood of oversmoothing due to the use of a product of two continuous covariates to describe the interaction between age at exposure and time, the final model allows for separate trends for each of three age-at-exposure groups (0–19, 20–39 and >40). As can be seen from Fig. 8, the fitted EARs decreased with time for survivors who were under 20 years ATB but were constant or increasing with time for survivors older ATB.

Table VII summarizes the observed and fitted values for the final AML model. Based on these data the model-based time-averagcd $ERR_{1\,Sv}$ is estimated to be 3.3. The corresponding EAR estimate is 1.1 cases per 10^4 PY Sv, and the $AR_{0.01\,Gy}$ is 46%.

Chronic Myelocytic Leukemia

Of the 62 cases that were eligible for inclusion in these analyses, 57 had DS86 kerma estimates less than 4 Gy and two had kerma estimates greater than 4 Gy (Table I). There were three additional first primary cases for whom a DS86 close estimate could not be computed.

Background rates. The increase in the background CML rates for this cohort is roughly proportional to attained age squared. Background rates differed significantly by sex (P = 0.008) with age-specific rates for women about 60% of those for men. The difference between the cities was even more pronounced (P = 0.003) with the rates in Hiroshima for either sex being more than three times those in Nagasaki (Fig. 9). There was no indication of a secular trend in the CML background rates, nor did the data suggest that the slope of the increase in the rates with attained age depended on either sex or city.

Excess risks. The CML data are consistent with a linear nonthreshold dose–response model. In particular, the excess risk exhibited a significant linear increase with dose (P < 0.001) that was not improved by the addition of either quadratic (P > 0.5) or spline (P > 0.5) terms in the weighted dose. The hypothesis of a 0.5-Gy threshold could be rejected for these data (P = 0.003).

The CML EARs have decreased rapidly with the passage of time (P <0.001). A log-linear ($e^{\beta t}$) model described this

TABLE VI
Acute Lymphocytic Leukemia, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (years)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	0	9	0	1	0	10
	Fitted background	0.26	0.23	0.72	0.66	0.98	0.89
	Fitted excess	0.06	7.84	0.01	0.90	0.07	8.74
20–39	Cases	0	0	2	1	2	1
	Fitted background	0.27	0.25	0.46	0.43	0.73	0.68
	Fitted excess	0.01	1.22	0.00	0.14	0.01	1.35
>=40	Cases	1	2	1	0	2	2
	Fitted background	0.68	0.64	0.41	0.40	1.09	1.04
	Fitted excess	0.00	0.73	0.00	0.05	0.00	0.78
All ages	Cases	1	2	3	1	4	3
	Fitted background	1.20	1.13	1.59	1.49	2.79	2.61
	Fitted excess	0.07	9.78	0.01	1.09	0.08	10.87
		Females					
0–19	Cases	0	5	3	1	3	6
	Fitted background	0.32	0.28	0.89	0.78	1.21	1.06
	Fitted excess	0.03	3.73	0.00	0.44	0.03	4.17
20–39	Cases	0	1	1	1	1	2
	Fitted background	0.66	0.65	1.33	1.29	1.99	1.94
	Fitted excess	0.01	1.37	0.00	0.16	0.01	1.53
>=40	Cases	1	2	0	0	1	2
	Fitted background	0.94	0.86	0.79	0.73	1.73	1.59
	Fitted excess	0.00	0.35	0.00	0.03	0.00	0.38
All ages	Cases	1	8	4	2	5	10
	Fitted background	1.92	1.79	3.01	2.80	4.93	4.59
	Fitted excess	0.04	5.44	0.00	0.63	0.04	6.07
		Both sexes					
All ages	Cases	2	10	7	3	9	13
	Fitted background	3.12	2.92	4.60	4.28	7.73	7.20
	Fitted excess	0.11	15.23	0.01	1.72	0.12	16.94

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

temporal trend somewhat better than did a power-function model (t^{β}). Although the temporal trend was not found to depend on age at exposure ($P > 0.5$), there were significant sex differences. Averaged over the follow-up period, men had greater excess risks ($P = 0.03$), and, after allowing for this difference, the temporal pattern of the excess risk was found to differ by sex ($P = 0.01$). As shown in Fig. 10, the fitted EAR for men had a high initial peak and has subsequently decreased rapidly with time, whereas the fitted EAR for women has stayed roughly constant over the years. These data also show a significant difference between the EARs for Hiroshima and Nagasaki ($P = 0.005$). The magnitude of the city effect was roughly proportional to that seen in the background risk, which suggests that differences in the number of excess cases for the two cities can be explained by differences in the Hiroshima and Nagasaki background rates.

Tables VIII and IX present expected numbers of cases based upon the final fitted model stratified by sex and city, respectively. The city difference is particularly striking since only 6 of the 57 CML cases were diagnosed in Nagasaki. On the basis of the

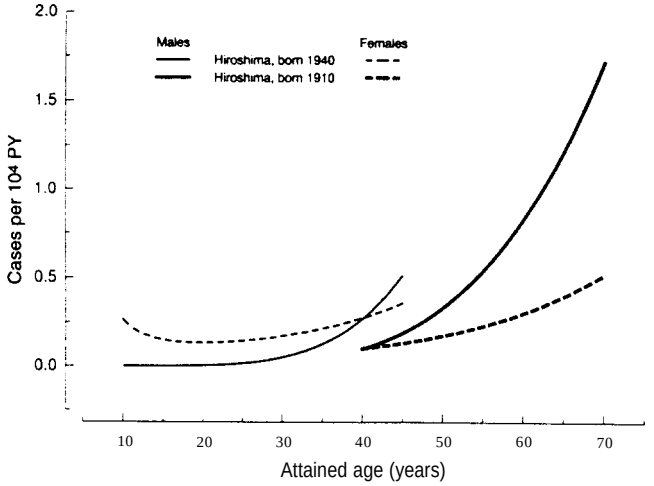

FIG. 7. Acute myelogenous leukemia—background rates. The fitted background rate for men and women in selected birth cohorts based on the model given in Appendix 1.

values in these tables we computed the time-averaged, model-based $ERR_{1\ Sv}$ as 6.2. The estimated EAR is 0.9 cases per 10^4 PY Sv, and the $AR_{0.01\ Gy}$ is estimated to be 62%.

Adult T-Cell Leukemia—Nagasaki

As indicated in Table X, 25 of the 43 cases not classified in one of the three subtypes considered thus far were diagnosed as ATL, and all except one of these cases occurred among Nagasaki survivors. In view of the differences between the two cities and because it is felt that radiation effects on ATL risk might differ from those on the risk of other types of leukemia, we analyzed the Nagasaki ATL data separately from the Hiroshima data for leukemias not classified as ALL, AML or CML. The ATL analyses were based on the 22 Nagasaki cases with DS86 dose estimates between 0 and 4 Gy.

It is well known that, as indicated by these data, ATL is endemic to Nagasaki and extremely rare in Hiroshima *(29).* However, it does seem surprising that ATL is virtually the only leukemia subtype other than ALL, AML or CML diagnosed among Nagasaki survivors. In fact only 2 of the 71 Nagasaki cases were other non-ATL leukemias. Data from the "open-city population" suggest that a slightly higher percentage, about 6%, of the Nagasaki cases with FAB diagnoses could not be classified as CML, AML, ALL or ATL *(17).*

Background rates. The background rates for ATL in Nagasaki rose rapidly with increasing attained age, but these rates did not appear to depend on either sex ($P > 0.5$) or birth cohort ($P = 0.15$) (Fig. 11).

Excess risks. There was no indication of a dose response for the Nagasaki ATL data. The point estimate of the EAR was negative with an estimated upper 95% confidence limit of 0.41 cases per 10^4 PY Sv. There was no statistically significant variation in ATL excess risk by sex or time since exposure.

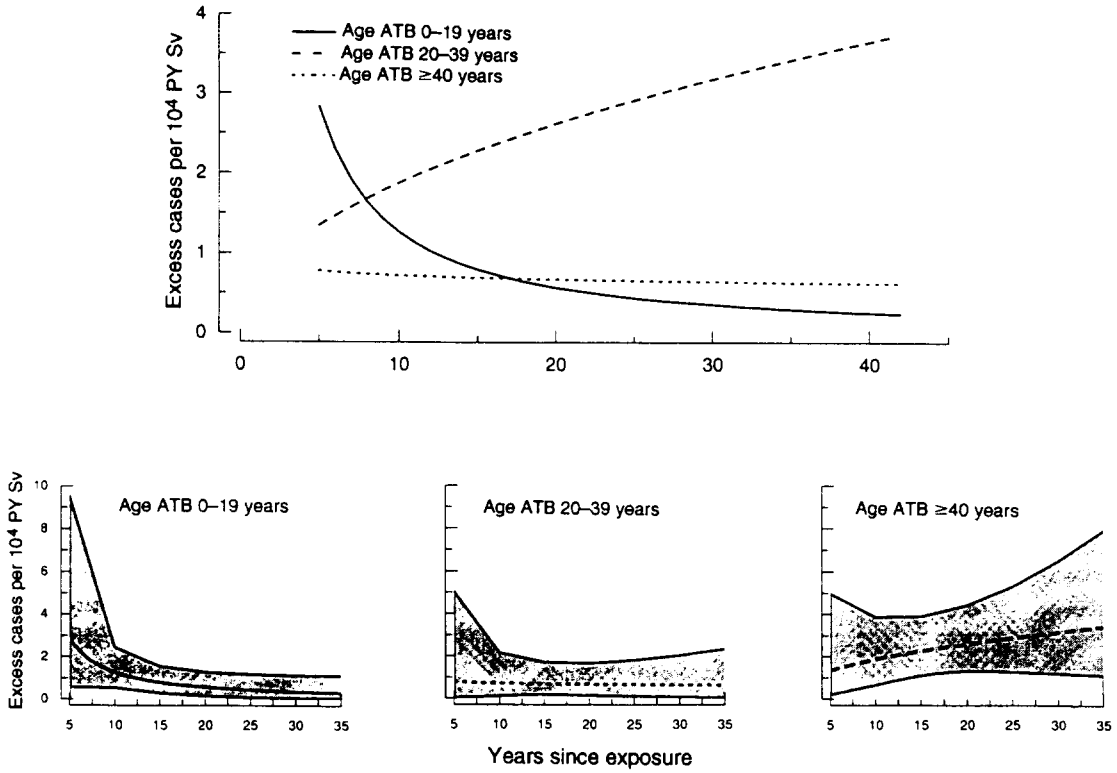

FIG. 8. Acute myelogenous leukemia—excess absolute risks. Fitted EAR estimates for survivors receiving 1-Sv bone marrow equivalent doses. Curves are shown for survivors at selected ages at exposure. The final model, shown in Appendix 1, did not depend on sex or city. The shaded areas in the lower panels indicate 95% confidence regions for the curves for males.

TABLE VII
Acute Myelogenous Leukemia, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

Age at exposure (year)	Dose category (Gy)	1950–1965		1966–1987		1950–1987	
		<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	0	4	5	5	5	9
	Fitted background	0.16	0.15	4.26	3.94	4.42	4.09
	Fitted excess	0.01	3.14	0.00	1.29	0.01	4.43
20–39	Cases	0	2	6	8	6	10
	Fitted background	0.96	0.88	5.27	4.92	6.23	5.80
	Fitted excess	0.00	0.94	0.00	0.95	0.00	1.89
>=40	Cases	4	7	6	6	10	13
	Fitted background	4.26	4.06	5.34	5.16	9.60	9.22
	Fitted excess	0.01	3.57	0.00	2.48	0.01	6.06
All ages	Cases	4	13	17	19	21	32
	Fitted background	5.38	5.09	14.88	14.02	20.26	19.11
	Fitted excess	0.01	7.65	0.01	4.73	0.02	12.38
		Females					
0–19	Cases	3	5	2	4	5	9
	Fitted background	1.63	1.45	3.92	3.45	5.55	4.90
	Fitted excess	0.01	3.72	0.00	1.55	0.01	5.26
20–39	Cases	2	3	6	6	8	9
	Fitted background	1.55	1.52	5.33	5.15	6.88	6.67
	Fitted excess	0.00	2.26	0.01	2.52	0.01	4.78
>=40	Cases	3	3	6	7	9	10
	Fitted background	2.03	1.86	3.02	2.78	5.05	4.64
	Fitted excess	0.01	3.69	0.01	3.75	0.02	7.45
All ages	Cases	8	11	14	17	22	28
	Fitted background	5.21	4.83	12.27	11.38	17.48	16.21
	Fitted excess	0.02	9.67	0.02	7.81	0.04	17.48
		Both sexes					
All ages	Cases	12	24	31	36	43	60
	Fitted background	10.60	9.93	27.15	25.40	37.74	35.33
	Fitted excess	0.04	17.32	0.03	12.54	0.06	29.80

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

Other Leukemias—Hiroshima

Of the 19 leukemia cases not classified as ALL, AML, CML or ATL, 17 were diagnosed in Hiroshima. Because of the small number of Nagasaki cases, the following analyses were limited to the 15 Hiroshima cases with DS86 dose estimates. These cases included 7 acute leukemias of unspecified type, 4 chronic lymphocytic leukemias, 2 myelodysplastic syndromes and 2 hairy-cell leukemias.

Background rates. Background rates for "other" leukemias in Hiroshima showed no significant dependence on attained age ($P > 0.5$) or birth cohort ($P = 0.14$). However, rates for males were estimated to be almost five times those for females ($P = 0.03$) (Fig. 11).

Excess risks. There was a significant linear dose response in the data for "other"' leukemias in Hiroshima ($P = 0.004$), but there was no evidence of nonlinearity ($P > 0.5$). The data did not suggest that the risk varied with either time since exposure ($P > 0.5$) or age at exposure ($P = 0.19$). However, the response was significantly different for men and women ($P = 0.03$). In particular, the estimated time-constant EAR for women was 0.44 (95% CI = 0.14–0.92) excess cases per 10^4 PY Sv, whereas the point estimate for men was negative with an estimated upper 95% confidence limit of 0.20 cases per 10^4 PY Sv.

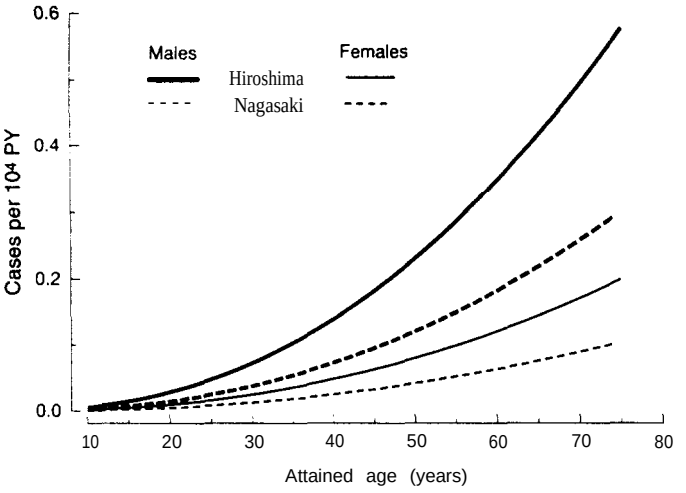

FIG. 9. Chronic myelogenous leukemia—background rates. The city-specific fitted background rate for men and women based on the model given in Appendix 1. There is no effect of birth cohort in this model.

Table XI presents observed and fitted values for the data for "other" leukemias for Hiroshima by sex. Using these data, the model-based sex- and time-averaged summary estimate of the $ERR_{1\ Sv}$ is 3.6, whereas the EAR and $AR_{0.01\ Gy}$ are estimated to be 0.21 cases per 10^4 PY Sv and 51%, respectively.

Leukemia Joint Analysis

The results of the type-specific leukemia analyses described above suggest that there are differences in the nature of the dose response for the leukemia types. These differences can be seen in Fig. 12, which compares the dose–response curves for the four diagnostic categories considered above, 5 and 35 years after exposure for three ages at exposure.

To examine this issue, we carried out a joint analysis of the data for AML, ALL and CML using the methods described by Pierce and Preston *(30)*. The joint analysis suggests that there are significant intertype differences in both

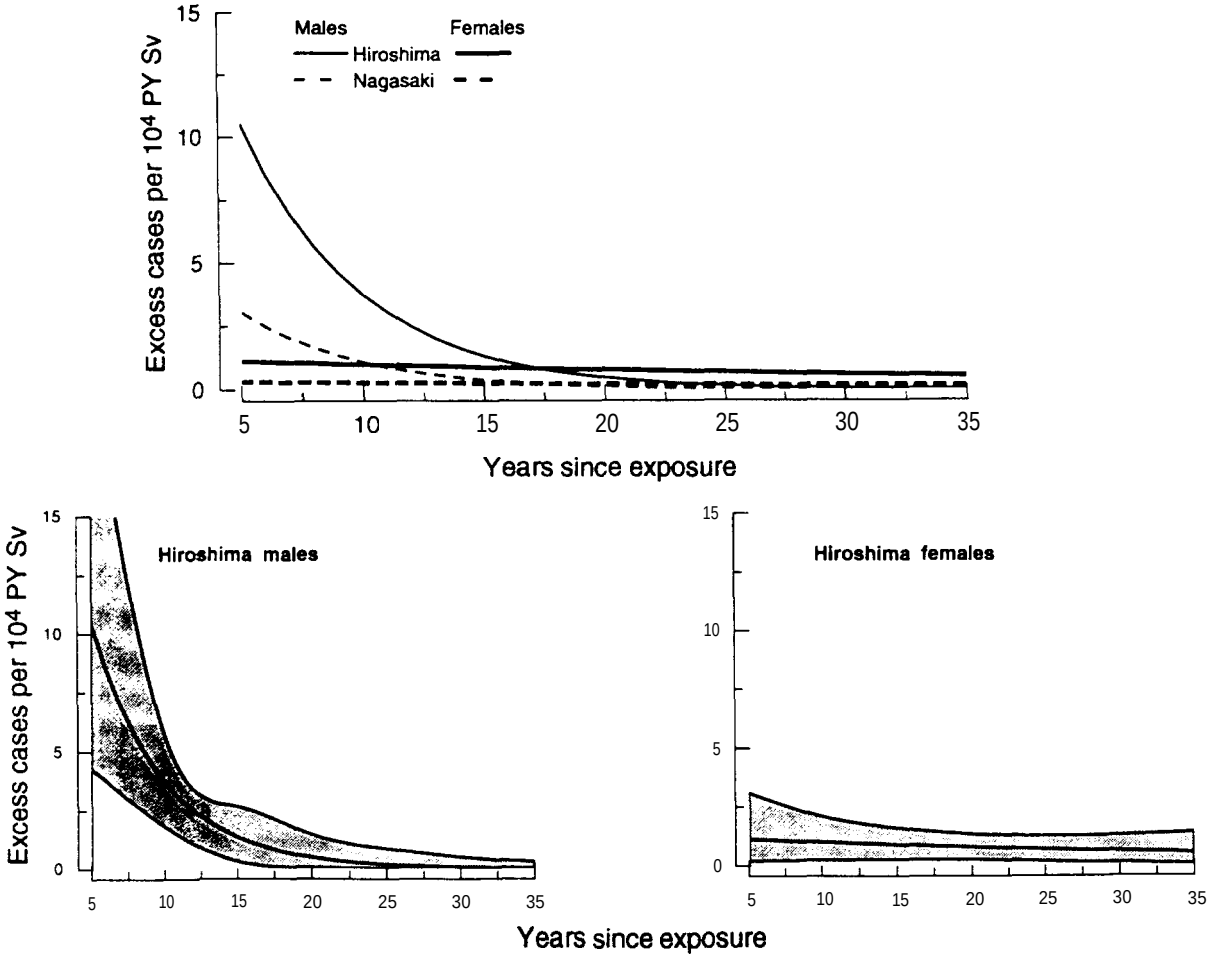

FIG. 10. Chronic myelogenous leukemia—excess absolute risks. Fitted EAR estimates for survivors receiving l-Sv bone marrow equivalent doses. Curves are shown for male and female survivors in each city. In the final model, shown in Appendix 1, the EAR does not depend on age at exposure. The lower panels display 95% likelihood-based confidence regions for the curves for Hiroshima.

TABLE VIII
Chronic Myelocytic Leukemia, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (year)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	1	6	2	1	3	7
	Fitted background	0.32	0.34	1.50	1.59	1.82	1.93
	Fitted excess	0.04	6.22	0.00	0.23	0.04	6.45
20–39	Cases	1	6	3	2	4	8
	Fitted background	0.64	0.67	1.45	1.54	2.09	2.22
	Fitted excess	0.01	3.02	0.00	0.11	0.01	3.13
>=40	Cases	0	6	2	1	2	7
	Fitted background	2.15	2.37	1.56	1.74	3.71	4.11
	Fitted excess	0.03	5.36	0.00	0.11	0.03	5.46
All ages	Cases	2	18	7	4	9	22
	Fitted background	3.11	3.38	4.51	4.88	7.62	8.26
	Fitted excess	0.08	14.59	0.00	0.45	0.08	15.04
		Females					
0–19	Cases	1	0	0	3	1	3
	Fitted background	0.22	0.22	1.01	1.00	1.23	1.21
	Fitted excess	0.01	2.23	0.01	1.79	0.03	4.02
20–39	Cases	0	2	3	4	3	6
	Fitted background	0.79	0.89	2.16	2.39	2.96	3.28
	Fitted excess	0.01	2.38	0.01	1.82	0.02	4.20
>=40	Cases	0	6	4	3	4	9
	Fitted background	1.59	1.67	1.58	1.67	3.17	3.34
	Fitted excess	0.01	1.74	0.01	0.78	0.02	2.52
All ages	Cases	1	8	7	10	8	18
	Fitted background	2.60	2.77	4.76	5.06	7.36	7.83
	Fitted excess	0.04	6.35	0.03	4.39	0.07	10.74
		Both sexes					
All ages	Cases	3	26	14	14	17	40
	Fitted background	5.71	6.15	9.27	9.94	14.98	16.09
	Fitted excess	0.12	20.94	0.03	4.84	0.15	25.78

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

the temporal pattern (P = 0.02, 2 df) and the nature of the variation of the risk with age at exposure (P = 0.002). After allowing for these differences a test for nonlinearity in the dose–response function, with a common amount of curvature for all three types assumed, was statistically significant (P = 0.008), whereas the test for type-specific differences in the shape of the dose–response function was not significant (P = 0.35, 2 df). Although the latter test is not powerful, this result suggests that the differences in the shape of the dose–response function described in the earlier sections should be interpreted with caution. There was strong evidence against a 0.5-Gy threshold (P <0.001).

A joint analysis of the data for ATL and "other" leukemias for the two cities suggested significant city differences in both the background rates and the EARs (P = 0.05, 5 df). The details of this analysis will not be presented here.

Lymphoma

A total of 210 lymphoma cases, including 22 Hodgkin's and 188 non-Hodgkin's cases, met the basic criteria for inclu-

TABLE IX
Chronic Myelocytic Leukemia, Distribution of Observed and Fitted Cases by City, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (year)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Hiroshima					
0–19	Cases	1	4	2	3	3	7
	Fitted background	0.42	0.49	2.01	2.32	2.44	2.81
	Fitted excess	0.05	7.47	0.01	1.80	0.06	9.27
20–39	Cases	1	8	5	6	6	14
	Fitted background	1.21	1.44	3.05	3.64	4.26	5.09
	Fitted excess	0.02	4.92	0.01	1.79	0.03	6.71
>=40	Cases	0	11	6	4	6	15
	Fitted background	3.13	3.76	2.66	3.20	5.80	6.96
	Fitted excess	0.03	6.69	0.00	0.84	0.04	7.54
All ages	Cases	2	23	13	13	15	36
	Fitted background	4.76	5.70	7.73	9.16	12.50	14.86
	Fitted excess	0.10	19.09	0.03	4.43	0.13	23.52
		Nagasaki					
0–19	Cases	1	2	0	1	1	3
	Fitted background	0.11	0.06	0.50	0.27	0.61	0.34
	Fitted excess	0.01	0.97	0.00	0.22	0.01	1.19
20–39	Cases	0	0	1	0	1	0
	Fitted background	0.22	0.12	0.56	0.29	0.79	0.40
	Fitted excess	0.00	0.48	0.00	0.14	0.01	0.62
>=40	Cases	0	1	0	0	0	1
	Fitted background	0.61	0.28	0.48	0.21	1.09	0.49
	Fitted excess	0.01	0.41	0.00	0.04	0.01	0.45
All ages	Cases	1	3	1	1	2	4
	Fitted background	0.94	0.46	1.54	0.78	2.48	1.23
	Fitted excess	0.02	1.85	0.00	0.41	0.02	2.26
		Both cities					
All ages	Cases	3	26	14	14	17	40
	Fitted background	5.71	6.15	9.27	9.94	14.98	16.09
	Fitted excess	0.12	20.94	0.03	4.84	0.15	25.78

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

sion in the analyses. The primary analyses were based on the 170 cases of non-Hodgkin's lymphoma (NHL) among survivors with DS86 kerma below 4 Gy. There were an additional 21 cases of Hodgkin's lymphoma in this group. Because of the small number of cases, detailed analyses of the Hodgkin's cases were not carried out.

Background rates. The increase in the NHL background rates was roughly proportional to the fourth power of attained age. Rates for women were about 60% of those for men ($P = 0.002$). The data suggested ($P = 0.01$) that age-specific background NHL rates have been increasing by about 3% per year over the course of this study (Fig. 13). Neither the rate of increase with attained age ($P = 0.4$) nor the secular trend ($P > 0.5$) appeared to depend on sex. Background rates for the two cities did not differ ($P = 0.4$).

Excess risks. The test for a linear dose response in the EAR model was not significant ($P = 0.09$), nor was the fit improved by the addition of a quadratic term in the dose ($P > 0.21$). An unconstrained sex-effect model could not be fitted because of the negative value of the excess risk for females. However, a model in which the EAR for females was constrained to be equal to zero fit significantly better

TABLE X
Distribution of ATL and Other Leukemia Types by City and Sex[a]

	Hiroshima		Nagasaki	
Type	Male	Female	Male	Female
ATL	0	1	9(1)	13 (1)
Non-ATL	7	8 (1)	1 (1)	0 (1)
Total	7	9(1)	9 (2)	l4 (2)

[a] Numbers of additional cases with unknown DS86 dose or DS86 kerma estimates greater than 4 Gy are given in parentheses.

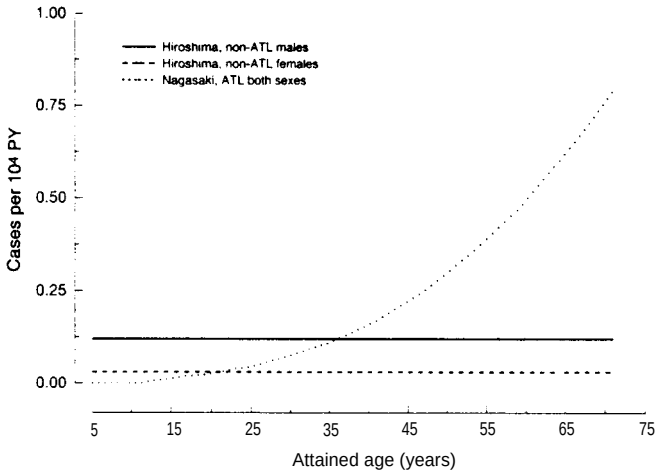

FIG. 11. Other leukemia types—background rates. Background rates for other types of leukemia, excluding ATL, for Hiroshima males and females and background ATL rates for both sexes in Nagasaki. The shaded areas in the lower panels indicate 95% confidence regions for the curves for Hiroshima.

than the simple linear dose–response model ($P = 0.04$). In view of the lack of significance of the test for a dose response it is better to consider a comparison with the no dose–response model based on two degrees of freedom. By this more stringent criterion these data still suggest a significant excess risk for males ($P = 0.03$, 2 df). The EAR did not appear to depend on time since exposure ($P > 0.5$), attained age ($P = 0.25$) or age at exposure ($P > 0.5$). Analyses of the lymphoma ERR failed to demonstrate a significant overall dose response ($P > 0.5$) or to provide evidence of a sex difference in the risks ($P = 0.3$). In the final model the time-constant EAR for men is estimated to be 0.56 cases per 10^4 PY Sv (95% CI = 0.08–1.39), whereas that for women is 0 with an upper 95% bound of 0.28 cases per 10^4 PY Sv. Based on the observed and fitted values summarized in Table XII the sex- and time-averaged model-based estimates of the $ERR_{1\ Sv}$, EAR and $AR_{0.01\ Gy}$ are 0.31, 0.22 cases per 10^4 PY Sv and 7.6%, respectively. If only data for males are used, the model-based estimates of the $ERR_{1\ Sv}$, EAR and $AR_{0.01\ Gy}$ are 0.62, 0.56 cases per 10^4 PY Sv and 14%, respectively.

EAR analyses of the Hodgkin's cases failed to demonstrate a significant dose response ($P > 0.5$). The sign of the dose coefficient was negative. When separate dose–response functions were allowed for men and women, the coefficient for men was positive whereas that for women was negative. However, there was no evidence of a significant dose response for either sex. An analysis of all lymphoma cases as a group led to essentially the same results as the NHL analyses described above.

Multiple Myeloma

As indicated in Table I, 73 cases of multiple myeloma were diagnosed among A-bomb survivors in the LSS between 1 October 1950 and the end of 1987. A relatively high proportion of these cases (8.6%) were classified as second primaries, compared to leukemia (2.8%) or lymphoma (3.1%). Among the 65 cases that met the basic inclusion criteria 59 had DS86 kerma estimates below 4 Gy.

Background rates. The increase in multiple myeloma background rates is proportional to the eighth power of attained age. This rapid increase is consistent with multiple myeloma being primarily a disease of old age. The LSS data also suggest that age-specific background rates have increased by about 5% per year over the course of this study ($P = 0.04$) (Fig. l4). Rates did not appear to differ by sex ($P = 0.4$) or city ($P > 0.5$).

Excess risks. When analyses were limited to first-primary multiple myeloma cases with DS86 estimates below 4 Gy kerma there was no evidence of a significant dose response ($P = 0.12$), nor was there any evidence of nonlinearity in the dose response ($P > 0.5$). The point estimate of the time-averaged EAR for this model was 0.08 cases per 10^4 PY Sv (95% CI < 0–0.3). The EAR did not appear to vary with sex ($P = 0.4$), time since exposure ($P = 0.4$), age at exposure ($P = 0.4$) or city ($P > 0.5$).

Because of the contrast between this finding and findings of recent mortality analyses based on death certificates *(13)* and an earlier incidence study *(5)*, both of which reported evidence of a radiation effect, differences between the earlier data sets and the present data were examined in detail. Four of the 36 cases in the data set in the LSS mortality report were excluded in the present analysis: three, with DS86 dose estimates of 0.15, 0.21 and 1.5 Gy, had been rejected by the leukemia registry, and one high-dose case (5.6 Gy) was a second primary. Nine cases were excluded from the mortality analysis because of unknown DS86 estimates. Recent extensions of the DS86 system made it possible to compute dose estimates for 6 of the 9 unknown-dose cases excluded from the mortality analyses, however; one of these cases (0.2 Gy) was a second primary. The present series includes 22 first- and 3 second-primary cases with DS86 estimates and 3 cases with unknown dose not included in the mortality series. Among the 22 new cases used in these analyses, 4 were diag-

TABLE XI
Other Leukemias—Hiroshima Only, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (year)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	1	0	0	1	1	1
	Fitted background	0.73	0.86	0.93	1.10	1.65	1.96
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
20–39	Cases	1	0	1	1	2	1
	Fitted background	0.35	0.41	0.38	0.45	0.73	0.86
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
>=40	Cases	2	0	0	0	2	0
	Fitted background	0.54	0.66	0.26	0.33	0.80	0.99
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
All ages	Cases	4	0	1	2	5	2
	Fitted background	1.61	1.93	1.58	1.88	3.19	3.81
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
		Females					
0–19	Cases	0	1	0	0	0	1
	Fitted background	0.18	0.21	0.24	0.27	0.42	0.48
	Fitted excess	0.01	0.91	0.01	1.14	0.01	2.05
20–39	Cases	1	0	1	3	2	3
	Fitted background	0.19	0.23	0.24	0.29	0.43	0.52
	Fitted excess	0.01	1.02	0.01	1.21	0.01	2.22
>=40	Cases	0	1	0	1	0	2
	Fitted background	0.16	0.19	0.11	0.13	0.27	0.31
	Fitted excess	0.00	0.76	0.00	0.51	0.01	1.26
All ages	Cases	1	2	1	4	2	6
	Fitted background	0.53	0.63	0.59	0.68	1.12	1.31
	Fitted excess	0.02	2.68	0.02	2.86	0.03	5.54
		Both sexes					
All ages	Cases	5	2	2	6	7	8
	Fitted background	2.15	2.56	2.16	2.56	4.31	5.12
	Fitted excess	0.02	2.68	0.02	2.86	0.03	5.54

[a] Because of the small number of cases in Nagasaki these analyses were restricted to Hiroshima. The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

nosed and died after 1985, 7 had not died by the end of follow-up, and 11 did not list myeloma as the primary cause of death. Only 4 of these cases had doses over 0.1 Gy, and the highest dose was 1.1 Gy.

Six of the 22 cases with known T65DR (T65D revised) doses used in the analyses of Ichimaru *et al. (5)* were not used in these analyses. These cases included one second primary (0.03 Gy), three cases rejected by the tumor registries and Leukemia Registry (DS86 dose estimates of 1.53 Gy, 0 Gy and unknown), an additional case for which a DS86 dose could not be computed, and one case with a DS86 kerma estimate greater than 4 Gy. The unused cases included three of the five high-dose cases (T65DR kerma greater than 1 Gy) in the Ichimaru series. The updated myeloma series contains 34 low-dose cases and only one new high-dose case diagnosed after 1976. The newly added high-dose case was a second primary with a DS86 kerma estimate greater than 4 Gy. This series also includes nine cases diagnosed before 1977 not included in the Ichimaru series. These cases all had DS86 kerma estimates below 1 Gy.

To obtain a better understanding of the impact of excluding the high-dose and second-primary cases, the EAR model

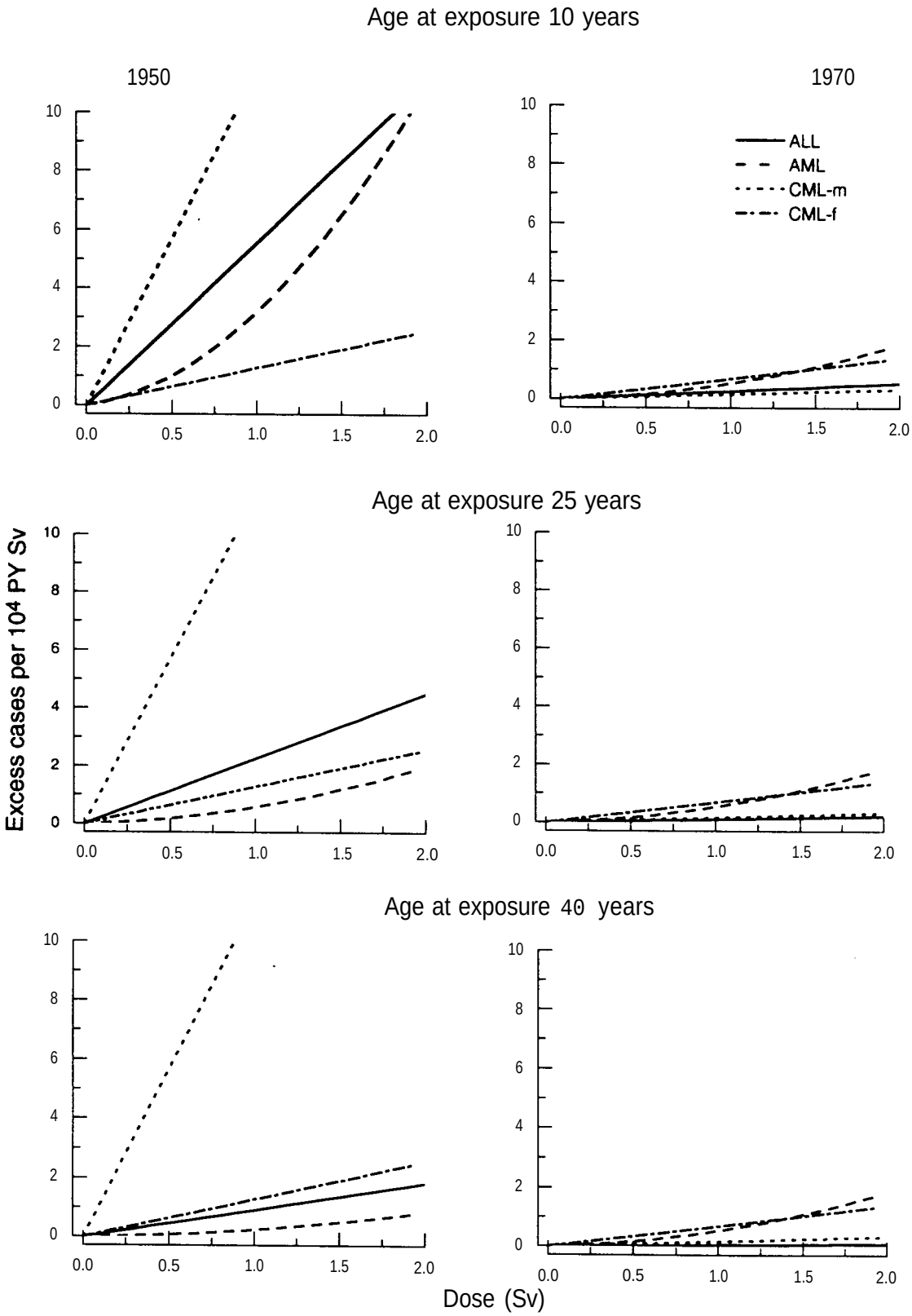

FIG. 12. Type-specific leukemia dose–response functions. The panels in this figure compare the dose–response functions for the major leukemia subtypes in 1950 (column 1) and 1970 (column 2) for survivors aged 10 (row 1), 25 (row 2) and 40 (row 3) at the time of exposure. The curves were computed from the models described in Appendix 1 by setting the time-since-exposure and age-at-exposure variables to the appropriate values.

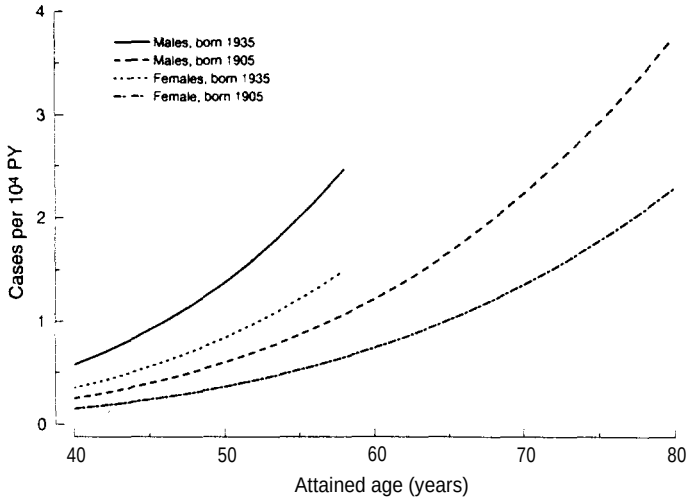

FIG. 13. Non-Hodgkin's lymphoma—background rates. The fitted background rate for men and women in selected birth cohorts based on the model given in Appendix 1.

was refitted using several expanded data sets. Including survivors with DS86 estimates over 4 Gy (one additional case and 6150 PY) had virtually no effect on the EAR or the significance level of the test ($P = 0.10$). Addition of the five second-primary cases with known dose also had little effect on the fit or the test for a dose response ($P = 0.09$). When both the second primaries and the case in the >4 Gy kerma group were included, the point estimate of the EAR increased to 0.12 and barely reached statistical significance ($P = 0.05$). Since the LSS mortality analysis was based on ERR models, we fitted ERR models to these data. Using the basic data set (first primaries with kerma under 4 Gy), the $ERR_{1\,Sv}$ point estimate of 0.25 was not significantly different from 0 ($P > 0.5$). However, addition of both the case in the >4 Gy kerma group and the second-primary cases increased the estimated $ERR_{1\,Sv}$ to 0.9 and was statistically significant ($P = 0.02$).

On the basis of these analyses, we feel that the current LSS incidence data provide little evidence for an increased risk of myeloma. Thus our final model for myeloma incidence assumes no effect of radiation exposure. Table XIII summarizes the observed and fitted numbers of cases using this model. Earlier results based on the mortality data appear to be heavily dependent on the inclusion of questionable diagnoses and of both high-dose cases and second primaries that have routinely been excluded in the current analyses of the incidence data. A detailed review of all of the lymphoma and myeloma cases is being planned. Perhaps this review, along with the extension of the follow-up period, will allow a more definitive statement about myeloma risks based on the LSS.

DISCUSSION

This report provides a comprehensive analysis of the incidence of leukemia, malignant lymphoma and multiple myeloma in the LSS between 1 October 1950 and the end of 1987, adding 9 years of follow-up for leukemia and 12 years for multiple myeloma since the last LSS incidence reports of these diseases *(5, 7)*. This is the first analysis of the LSS incidence data for malignant lymphoma. The unified approach to identification and classification of cases using data from all relevant sources and the use of new statistical methods *(10)* have made possible more detailed and quantitative analyses than were possible in the past.

The principal finding of the leukemia analyses was that the risk associated with radiation exposure varied significantly among the various types of leukemia. The magnitude of risk exhibited statistically significant and often complex variability with time since exposure, age at exposure and, to a somewhat lesser extent, sex. These findings clearly demonstrate that leukemia risk estimates used for risk assessment and the comparison of various populations should allow for the effects of age, time and sex on the excess risk. Summary risk estimators that do not allow for these important factors can be misleading.

The present analyses emphasize the importance of allowing for background incidence rates when assessing radiation-induced leukemia risks. In particular, it is essential to recognize the differences between Hiroshima and Nagasaki CML and ATL baseline rates when interpreting the data on excess risks for these subtypes. Earlier misunderstandings of the nature of the excess risks for the two cities arose because intercity differences in background rates were not considered. Although the LSS data are of limited use for detailed analyses of background rates because of the nature of the cohort, it is noteworthy that these data do not provide evidence of an elevated background rate for ALL for the youngest survivors. This finding is consistent with other reports on the incidence of ALL in Japan *(31, 32)*. Recently, Bessho *(33)* has suggested that this observation may be a result of misclassification of ALL in Japanese children. However, in view of the generally high diagnostic standards of the Leukemia Registry, which has included reviews by Japanese and U.S. hematologists and the recent Leukemia Registry–FAB review of the Leukemia Registry materials, misclassification seems less likely for these data.

Two questions regarding the temporal pattern of leukemia risks after radiation exposure are of interest. The first concerns estimates of the excess leukemia risk among the A-bomb survivors during the 5 years before the initiation of follow-up of the LSS cohort. The second concerns the evidence for an excess risk of leukemia in recent years. Because of problems with case ascertainment and determination of the population size it is not possible to compute risk estimates for the years before 1948, but Folley *et al. (2)* evaluated leukemia incidence in Hiroshima and Nagasaki between 1948 and 1950 in relation to distance from the hypocenter. In their study, cases were obtained from the Leukemia Registry but not classified by type. Population estimates were based

TABLE XII
Non-Hodgkin's Lymphoma, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (year)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	3	5	6	8	9	13
	Fitted background	0.87	0.82	10.05	9.23	10.93	l0.05
	Fitted excess	0.01	1.38	0.01	1.71	0.02	3.10
20–39	Cases	4	2	9	10	13	12
	Fitted background	2.34	2.16	9.19	8.60	11.54	10.77
	Fitted excess	0.00	0.67	0.00	0.71	0.01	1.38
>=40	Cases	7	3	12	13	19	16
	Fitted background	8.03	7.65	8.69	8.39	16.71	16.04
	Fitted excess	0.01	0.98	0.00	0.47	0.01	1.45
All ages	Cases	14	10	27	31	41	41
	Fitted background	11.24	10.63	27.94	26.23	39.18	36.86
	Fitted excess	0.02	3.03	0.02	2.89	0.04	5.93
		Females					
0–19	Cases	2	0	8	4	10	4
	Fitted background	0.72	0.63	7.83	6.83	8.55	7.46
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
20–39	Cases	3	4	19	18	22	22
	Fitted background	3.36	3.31	16.34	15.84	19.70	19.15
	Fitttd excess	0.00	0.00	0.00	0.00	0.00	0.00
>=40	Cases	6	4	15	5	21	9
	Fitted background	6.90	6.30	10.39	9.55	17.29	15.85
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
All ages	Cases	11	8	42	27	53	35
	Fitted background	10.97	10.24	34.56	32.23	45.54	42.46
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
		Both sexes					
All ages	Cases	25	18	69	58	94	76
	Fitted background	22.21	20.87	62.50	58.45	84.71	79.32
	Fitted excess	0.02	3.03	0.02	2.89	0.04	5.93

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

on the 1950 census of atomic bomb survivors subsequently used in the definition of the LSS cohort. The results of Folley *et al.* provide clear evidence of an increased risk of leukemia among proximally exposed (less than 2000 m from the hypocenter) survivors.

To compare the risk estimates of Folley *et al.* with those seen in the first few years of follow-up of the LSS, we constructed a special data set. Cases and person-years for the period from 1 October 1950 through 31 December 1953 were cross-classified by sex, city and distance with the categories used by Folley *et al.* Table XIV compares the populations and crude estimates of the risk derived from the data of Folley *et al.* with estimates based upon the LSS data. The results of Folley *et al.* appear to underestimate the incidence for distal survivors, especially in Nagasaki. There may also be some under-ascertainment of cases among the Hiroshima proximal survivors. Despite the problems with case ascertainment and population definition, leukemia risks averaged over the 3 years before the start of the LSS appear to have been elevated. The report of Folley *et al.* suggests that the largest excess risks are seen in survivors under the age of 45 at the time of exposure and that CML accounts for a substantial fraction of the early excess risk.

These findings are consistent with the results of our analyses of the first years of follow-up in the LSS. This comparison highlights an important limitation of the LSS leukemia data:

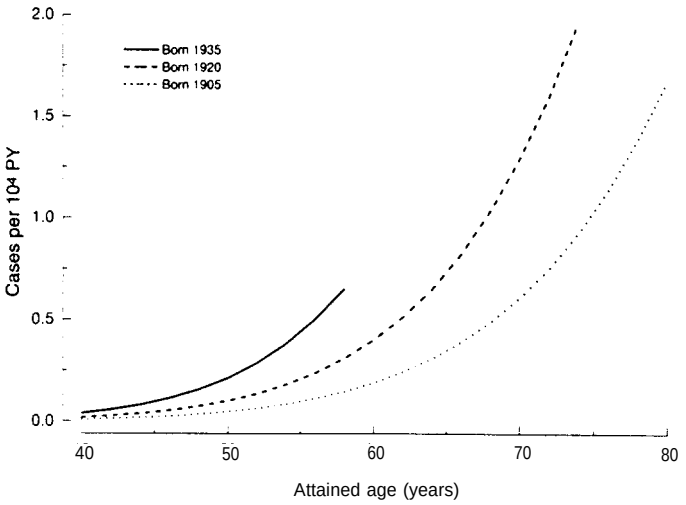

FIG. 14. Multiple myeloma—background rates. The fitted background rate for selected birth cohorts based on the model given in Appendix 1.

data for the first 5 years of follow-up are not incuded. Assuming the 1948–1950 risks are of the size suggested by the data of Folley *et al.*, it is clear that a significant number of excess cases are not included in the LSS. Crude calculations suggest that inclusion of the early years of follow-up would increase the average leukemia risk estimates (all types) given earlier in this report by about 10 to 15%. If the risk models in this report were to be used for other populations, bounds on the risk could be obtained by allowing the EAR to increase linearly from zero at 2 years after exposure to the model estimate at 5 years after exposure or by considering the risk to be equal to the 1950 value for the period from 2 to 5 years after exposure.

The issue of whether or not an increased risk of leukemia is seen 30 or more years after exposure has received much attention. To address this question, supplementary analyses of the pooled data for the period from 1976 through 1987 were carried out. A total of 72 cases occurred: 39 among survivors exposed to less than 0.01 Gy and 33 among those with higher doses. A significant linear dose response was apparent ($P = 0.005$), and addition of a quadratic term in the weighted dose did not improve the fit ($P = 0.3$). The model for the pooled leukemia data predicts about 7 excess cases among the 33 cases that occurred among survivors with doses over 0.01 Gy. There was a weak suggestion of heterogeneity in the EAR with age ATB ($P = 0.07$). The largest excess risks appeared to have occurred among survivors who were under 20 or over 40 years old ATB with little, if any, excess risk apparent for survivors who were 20 to 39 years old ATB. These findings indicate the importance of continued follow-up. The EAR during the last 12 years of follow-up did not appear to vary with time since exposure ($P > 0.5$) or sex ($P > 0.5$). However, there was a significant city difference ($P = 0.03$), with Nagasaki risks being less than those in Hiroshima. Indeed the point estimate of the Nagasaki EAR for this period was negative, though not significantly so. Because of differences in the types of leukemia seen in the two cities, particularly the relatively large number of ATL cases in Nagasaki, and the differences in temporal patterns and levels of excess risk for the leukemia types, the city difference should be interpreted with caution.

Among the three major types of leukemia associated with radiation, ALL and CML (at least for males) share similar responses characterized by a linear, nonthreshold dose response and an initial high risk (in 1950) followed by a gradual decline. However, as noted in the presentation of the results of the joint analysis, there is no strong evidence against a null hypothesis of equal curvature for the ALL, AML and CML dose responses. Our results also suggest that there are detectable excess risks for leukemia at doses below 0.5 Gy. Based upon a proportional incidence analysis of the Leukemia Registry data, Tomonaga *et al. (17)* suggested previously that the CML dose response is well described by a linear, nonthreshold function. As noted above, our results are not inconsistent with theirs. However, the risks at very low doses predicted by the models considered here are much lower than those suggested in the crude incidence analysis of the earlier paper.

The present analysis also clearly indicates that the EAR for CML is higher in Hiroshima than in Nagasaki, but this difference appears to be proportional to the differences in the background rates. Unlike ALL and CML, the risk for AML risk is better described by a nonlinear response with a tendency to decrease with time for younger survivors but remain stable or possibly increase for older survivors. The temporal pattern for AML among survivors exposed as adults resembles that which has generally been found for solid tumor incidence *(20)*. The various temporal patterns found for the three leukemia types were generally consistent with the schematic summary of leukemia risks presented in previous reports *(4, 7)*. Our analyses found a significant difference in the temporal pattern of the CML excess risks for men and women, especially in the early years of follow-up. But, because of the small number of cases, it is possible that this is a chance finding. Since the RERF data cannot shed additional light on this question, data from other populations should be examined to determine if there is evidence for a similar interaction between sex and time in the excess risks for CML.

Further studies are necessary to investigate possible biological and epidemiological bases for age, sex and time differences in the type-specific patterns of leukemia EARs. A link between CML and ALL is suggested by the Philadelphia chromosome, or variants of translocation involving the *bcr* and *abl* genes, present in almost all CML cases and some ALL cases *(34)*. Ionizing radiation was shown to produce a number of chromosomal abnormalities, including changes morphologically similar to the Philadelphia chromosome, in

TABLE XIII

Multiple Myeloma, Distribution of Observed and Fitted Cases by Sex, Time, Exposure Status and Age at Exposure[a]

		1950–1965		1966–1987		1950–1987	
Age at exposure (year)	Dose category (Gy)	<0.01	0.01–4	<0.01	0.01–4	<0.01	0.01–4
		Males					
0–19	Cases	0	0	2	2	2	2
	Fitted background	0.02	0.02	1.46	1.36	1.48	1.38
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
20–39	Cases	0	0	4	4	4	4
	Fitted background	0.20	0.18	2.96	2.75	3.16	2.93
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
>=40	Cases	0	2	4	4	4	6
	Fitted background	1.47	1.39	3.64	3.52	5.11	4.91
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
All ages	Cases	0	2	10	10	12	12
	Fitted background	1.68	1.59	8.06	7.63	9.74	9.22
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
		Females					
0–19	Cases	0	0	0	2	0	2
	Fitted background	0.03	0.02	2.01	1.74	2.03	1.76
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
20–39	Cases	1	3	6	3	7	8
	Fitted background	0.44	0.44	8.57	8.32	9.01	8.76
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
>=40	Cases	0	2	12	8	12	10
	Fitted background	2.13	1.93	7.52	6.90	9.65	8.83
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
All ages	Cases	1	5	18	13	19	18
	Fitted background	2.59	2.39	18.10	16.96	20.69	19.35
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00
		Both sexes					
All ages	Cases	1	7	28	23	29	30
	Fitted background	4.28	3.98	26.16	24.59	30.43	28.57
	Fitted excess	0.00	0.00	0.00	0.00	0.00	0.00

[a] The fitted value for the background cases is the number of cases predicted by the final model assuming no radiation exposure. The fitted value for the excess cases is computed as the difference between the estimated number of background cases and the total number of cases predicted by the model. The specific model used is presented in Appendix 1. The only constraint in these fitted values is that the total number of fitted (background plus excess) cases equal the total number of observed cases.

apparently healthy subjects *(35)*, and X irradiation *in vitro* was found to induce *bcr-abl* fusion genes, including the types specific to CML (Ito, personal communication). Studies are under way to investigate molecular changes, including *bcr-abl* fusion genes in exposed and nonexposed leukemia cases. The translocation involving the *bcr* and *abl* genes has rarely been found in AML cases, but epidemiological studies, including a case-control study of the A-bomb survivors *(36)*, demonstrated that exposure to benzene increases the risk of leukemia, especially AML *(37)*. In trying to learn about mechanisms of radiation leukemogenesis, especially for AML, it would be important to consider the possible effect of other leukemogenic factors, such as benzene and other chemical agents. Although certain cytogenetic effects caused by radiation may be sufficient for the induction of some types of leukemia such as CML and ALL, additional changes might be necessary for other types such as AML in adults.

Nagasaki is an endemic area of HTLV-1, an endogenous virus known to cause ATL. Roughly 30% (22 out of 58) of the Nagasaki leukemia cases were diagnosed as having ATL, whereas less than 1% (1 out of 173) of the leukemias in Hiroshima were ATL. The failure to find a significant radiation effect for ATL suggests that radiation exposure does not interact with HTLV-1 in inducing ATL. Recent data also

TABLE XIV
Early Leukemia Deaths, Comparison of the 1948–1950 Data of Folley *et al.* and 1950–1953 Data of the Life Span Study (LSS)[a]

		LSS population, 1950–1953					Open population (Folley *et al.*), 1948–1950				
Distance		Population	Person years	Cases	Crude rate per 1,000,000 people	Crude rate per 10,000 PY	Population	Person years (approximate)	Cases	Crude rate per 1,000,000 people	Crude rate per 10,000 PY
Proximal 0–1999 m	Hiroshima	26,163	83,723	27	1,032	3.22	30,998	96,714	15	484	1.55
	Nagasaki	7,648	24,485	7	915	2.86	8,259	25,768	7	848	2.72
	Total	33,811	108,208	34	1,006	3.14	39,257	122,482	22	560	1.80
Distal >=2000 m	Hiroshima	35,805	114,297	5	140	0.44	67,267	209,873	4	59	0.19
	Nagasaki	24,079	76,828	3	125	0.39	88,703	276,753	3	34	0.11
	Total	59,884	191,125	8	134	0.42	l55,970	486,626	7	45	0.14
Total	Hiroshima	61,968	198,020	32	516	1.62	98,265	306,587	19	193	0.62
	Nagasaki	31,727	101,313	10	315	0.99	96,962	302,521	10	103	0.33
	Total	93,695	299,333	42	448	1.40	195,227	609,108	29	149	0.48

[a] The data for cases and persons at risk in the open population for the period from 1 January 1948 through 31 December 1950 were taken from Folley *et al. (2).* The population size was determined from the 1950 census of A-bomb survivors. Person-years were estimated as 3.12 times the population size. The 4% correction was used to allow for deaths during the 3-year follow-up period. The magnitude of this correction was estimated using the LSS data. The LSS data cover the period from 1 October 1950 through 31 December 1953.

show that HTLV-1 infection rates are not associated with exposure to A-bomb radiation (Matsuo, personal communication). As a result of the Leukemia Registry–FAB reclassification, most of the cases previously classified as CLL or "lymphosarcoma leukemia," including many of the cases considered in the earlier report on CLL by Finch and Hoshino *(38),* are now classified as ATL. After the Leukemia Registry–FAB reclassification there were only four CLL cases in the LSS *(17).* The small number of CLL cases is consistent with the rarity of this type of leukemia in the general Japanese population *(39, 40).*

After exposure to ionizing radiation, significant excesses of all types of leukemia, excluding CLL, have been reported consistently for almost 50 years *(41–46).* In the aggregate, studies of the association between leukemia and external exposure to low-LET radiation delivered at high dose rates demonstrate that leukemia should be considered separately from solid cancers because both the magnitudes of the risk and the risk patterns differ.

Although many studies have demonstrated an excess of radiogenic leukemia, few have sufficient data to evaluate the shape of the dose–response curve or provide detailed information about temporal trends or effect modification *(47–52).* The response appears to flatten at high doses, presumably due to cell-killing effects, but the small number of cases suggests caution in interpretation of the findings. Unlike solid tumors, radiogenic leukemias start to occur about 2 years after exposure. Excess absolute and relative risks generally appear to reach a peak soon thereafter and then gradually decline. Among adults exposed to radiation a positive association between leukemia risk and age at irradiation has been reported among the patients with anklosing spondylitis *(53)* and among women treated for benign gynecological diseases *(46, 54).* The results of our study are generally in line with other studies.

A statistically significant increased risk of multiple myeloma associated with exposure to A-bomb radiation has been reported in previous analyses of LSS mortality and incidence data *(5, 14, 55).* The magnitude of risk estimated was quite large, exceeded only by that for leukemia. The present study did not provide evidence of such an association. As described in the Results, the change is due primarily to increased follow-up, but differences in diagnostic criteria and the decision to consider only first-primary cancers also affected the risk estimates. The decision to limit analyses to cohort members with DS86 kerma estimates below 4 Gy did not have a major impact on the findings. It is noteworthy that no new cases of multiple myeloma were identified in the high-dose group during the last 12 years of follow-up. One might argue that misclassification or underdiagnosis of multiple myeloma has contributed to the above observation, but this seems unlikely in view of the general improvement in diagnostic procedures and inclusion of cases from all available sources. Earlier results based on the mortality data are dependent on the inclusion of misclassified cases, second primaries and cases with dose estimates over 4 Gy. A detailed review of the cases of multiple myeloma will be undertaken soon. Together with the extension of the follow-up period, this review should help clarify the nature of the risk of multiple myeloma in the LSS.

Like CLL, multiple myeloma is a malignant proliferative disorder of B-cell lineage and is considered to originate in terminally differentiated B lymphocytes. In view of the lack of evidence for a relationship between radiation exposure

and CLL it may not be surprising that radiation is not related to multiple myeloma. Epidemiological studies of populations with protracted low-level radiation exposures have suggested an increased risk of multiple myeloma *(56, 57)*. It is possible, though unlikely, that protracted exposures produce multiple myeloma but not leukemia *(45)* or that the reported effects reflect confounding or other mechanisms. The most recent analysis of mortality of Hanford workers provides less evidence than previously for increased risk of multiple myeloma associated with radiation dose *(58, 59)*.

For malignant lymphoma, limited evidence suggesting an excess risk associated with A-bomb radiation was available from early prevalence studies *(18, 19, 60)*, but mortality data have not demonstrated an association *(14)*. In the literature, there is reasonable agreement that Hodgkin's disease is not increased in irradiated populations *(41)*, but findings regarding NHL are variable. Increased risks were found in women treated with radiation for ankylosing spondylitis *(44)* or for cervical cancer *(61)*. Increased mortality from lymphosarcoma was found in early cohorts, but not in recent cohorts, of American radiologists *(62)*. No increased risk for NHL was reported from a recently updated and expanded study of women treated with radiation for various gynecological disorders *(54)* or of Chinese radiation workers *(63)*. The present finding of an increased risk of NHL, apparently limited to males, warrants further careful study. It might be argued that this finding reflects a bias arising from the inclusion of malignant lymphoma cases identified at autopsy. However, this seems unlikely since there is no evidence for time trends in the excess risk. Since Hodgkin's disease is relatively infrequent in the LSS, it is difficult to reach any conclusions about the effects of radiation on Hodgkin's disease. More definitive evidence on this issue is expected from a study now in progress involving standardized reviews of the LSS lymphoma cases. In speculating on mechanisms for a weak association between radiation and NHL, as suggested by the present data, it is of interest to note recent findings suggesting immune disturbance, as indicated by an increased prevalence of Epstein-Barr virus reactivation, associated with A-bomb radiation *(64)*.

A major difficulty in long-term follow-up studies such as this one involves consistency in the classification of outcomes in the face of changes in diagnostic procedures, criteria and nomenclature. The leukemia analyses in this study benefited greatly from the recently completed Leukemia Registry–FAB reclassification. Leukemia Registry–FAB diagnoses were available for more than 60% of the leukemia cases, whereas diagnoses in the remaining cases were based on supplementary reviews of available records by study hematologists. Although differences in diagnostic criteria may introduce some biases into type-specific analyses, these effects are not large since the availability of Leukemia Registry–FAB diagnoses appears to be independent of dose *(17)*. Furthermore, the changes in diagnosis resulting from the Leukemia Registry–FAB reclassification involved changes of specific diagnoses within the broad leukemia types considered here.

Although we reviewed the records carefully, the diagnoses of multiple myeloma and lymphoma in this study were not based on the kind of definitive consideration of all available materials involved in the Leukemia Registry–FAB review. Therefore, we chose to place less emphasis on subtype-specific analyses of these cancers in this report. Extensive re-examination of the material available for these sites is currently under way, and detailed reports are forthcoming. These more detailed analyses should provide additional insights into radiation effects for these cancers, but it is unlikely that the general conclusions regarding multiple myeloma and lymphoma in this paper will be affected in any substantive way.

Although much has been learned from these data, the next 10 to 20 years will be important in understanding the risks of radiation-induced hematopoietic tumors and lymphomas. The temporal pattern of leukemia risks, especially AML, among young survivors remains to be studied in detail. Also of interest are whether the relatively constant excess absolute risk of lymphoma in males persists and whether there are detectable differences in the risk of Hodgkin's disease and NHL.

APPENDIX 1

Ascertainment of LSS Leukemia, Lymphoma and Myeloma Cases

A master list of potential cases was created by merging (1) Leukemia Registry records for members of the LSS, (2) relevant tumor registry records for LSS cohort members, (3) information on deceased persons in the LSS whose cause of death as coded on the death certificate was a diagnosis of interest, and (4) information obtained from recent special reviews of myeloma cases. An initial review revealed that all death certificate cases not included in either the Leukemia Registry or tumor registries had previously been reviewed and rejected by either the Leukemia Registry or tumor registries. The master list contained 1233 individuals (including 197 people who were NIC ATB). Table AI summarizes the cases in the master list by ascertainment source and diagnostic category.

The 445 Leukemia Registry noncancer cases that were not included in the tumor registries as hematopoietic cancers or lymphomas were excluded from additional review. The remaining 788 cases were each broadly classified as a leukemia, lymphoma or myeloma, and the diagnoses were compared. As the data in Table AII indicate, there were some discrepancies between the two sources, due primarily to the differing coverage periods for the two registries and a lag in the processing of Leukemia Registry cases accessed during the 1980s. The data for discordant pairs were reviewed by the authors (S. K. and K. M.) to determine the final diagnosis. A special review of myeloma diagnoses found to differ from those used in earlier analyses was carried out by hematologists affiliated with the Leukemia Registry.

TABLE AI
Comparison of Tumor Registry and Leukemia Registry Cases[a]

	Tumor registry			
Leukemia registry	Lymphoma or hematopoietic cancer	Other cancer	Not included	Total
Cancer	541	12	104	657
Noncancer	19	104	341	464
Not included	112	—	—	112
Total	672	116	445	1233

[a] This table contains information on potential cases of leukemia, lymphoma or multiple myeloma identified from tumor registry (TR), leukemia registry (LR) or mortality surveillance records. Data on 197 NIC members of the LSS are included in the table. The 445 cases not classified as a disease of interest in any registry were excluded from further consideration. This group includes five death-certificate-only cases that were rejected in earlier LR reviews.

TABLE AII
Comparison of Tumor Registry and Leukemia Registry Diagnoses[a]

	Tumor registry diagnosis				
Leukemia registry diagnosis	Leukemia	Lymphoma	Myeloma	Other or not included	Total
Leukemia with FAB	136	12	0	39	187
Leukemia without FAB	96	11	0	26	133
Lymphoma	0	202	0	31	233
Myeloma	0	0	84	20	104
Other/not included	18	93	20	0	131
Total	250	318	104	116	788

[a] The comparison is based on broad diagnostic categories defined at an early stage in the review process. Leukemia cases from the leukemia registry with and without Leukemia Registry–FAB classification are treated separately. This table contains data on 126 NIC members of the LSS.

To compare the Leukemia Registry and tumor registry diagnoses at a more detailed level, cases were classified using ICD-O morphology codes *(23).* Table AIII shows the correspondence between FAB classifications, the traditional Leukemia Registry leukemia diagnostic categories, and the ICD-O morphology codes used in this study. When there was a discrepancy, and a Leukemia Registry–FAB diagnosis was available, it was chosen as the final diagnosis.

TABLE AIII
Comparison of Leukemia Diagnostic Categories[a]

Diagnostic category	ICDO-M	Leukemia registry reclassification category (Leukemia Registry–FAB)	Original leukemia registry type
Acute lymphocytic leukemia (ALL)	98213 Subacute lymphoid leukemia	Acute lymphocytic leukemia Lymphocytic leukemia types I and II	Acute lymphocytic leukemia
Acute myelogenous leukemia (AML)	98403 Erythroleukemia	Myeloid leukemia type VI	Erythroleukemia
	98613 Acute myeloid leukemia	Acute myeloid leukemia Myeloid leukemia types I, II and IV Acute leukemia NOS	Acute granulocytic leukemia Acute myelomonocytic leukemia
	98623 Subacute myeloid leukemia	Refractory anemia with excess blasts (RAEB) RAEB-T cell	
	98643 Aleukemic myeloid leukemia	Hypoplastic leukemia	
	98663 Acute promyelocytic leukemia	Myeloid leukemia type III	
	98913 Acute monocytic leukemia	Myeloid leukemia type V	Acute monocytic leukemia
Chronic myelogenous leukemia (CML)	98633 Chronic myeloid leukemia	CML Chronic myelomonocytic leukemia	Chronic granulocytic leukemia
	98653 Neutrophilic leukemia		
Adult T-cell leukemia (ATL)	97023 ATL	ATL	Leukosarcoma
Chronic lymphocytic leukemia (CLL)	98303 Plasma-cell leukemia	Plasma-cell leukemia	
	98233 CLL		CLL
Other leukemias	98013 Acute leukemia NOS	Acute leukemia NOS	Acute stem cell undifferentiated leukemia Acute leukemia NOS
	98603 Myeloid leukemia NOS		
	98003 Leukemia NOS		Leukemia NOS
	99403 Hairy-cell leukemia	Hairy-cell leukemia	
Myelodisplasia syndrome (MDS)	99601 MDS	Refractory anemia	

[a] This table summarizes the correspondence between ICD-O morphology codes, Leukemia Registry–FAB diagnostic categories, and the original Leukemia Registry type codes. During the review ICD-O morphology codes were assigned to every case. The final categorization of cases was based upon these codes.

TABLE AIV
Summary of Final Diagnoses by Source and Period[a]

Diagnosis	Period	Leukemia registry only	Both leukemia registry and tumor registry	Tumor registry only	Total
Leukemia	1946–1958	49	37	0	86
	1958–1980	12	173	0	185
	1981–1989	4	49	15	68
	Total	65	259	15	339
Lymphoma	1946–1958	15	18	0	33
	1958–1980	1	154	23	187
	1981–1989	1	37	46	84
	Total	17	209	78	304
Myeloma	1946–1958	1	0	0	1
	1958–1980	0	50	2	52
	1981–1989	1	31	9	41
	Total	2	81	11	94

[a] The 737 cases identified in the review are classified by the date of diagnosis and the availability of tumor registry or leukemia registry data. This table includes information on 117 NIC members of the LSS cohort.

TABLE AV
Reclassified (Leukemia Registry–FAB) Diagnoses and Final Leukemia Diagnoses in This Study[a]

Leukemia subtype	Leukemia Registry–FAB diagnosis: Yes	No	Total
AML	59 (57%)	44 (43%)	103
ALL	22 (69%)	10 (31%)	32
CML	43 (75%)	14 (25%)	57
ATL	12 (52%)	11 (48%)	23
Other	4 (25%)	12 (75%)	16
Total	140 (61%)	91 (39%)	231

[a] The distribution of Leukemia Registry–FAB diagnoses for the leukemia subtypes is described for the 231 cases used in the primary analyses for this paper.

Discrepant cases with no Leukemia Registry–FAB diagnosis were reviewed individually, and a consensus diagnosis was made. For 34 cases the tumor registry and Leukemia Registry diagnosis dates differed by more than 1 year. These cases were all reviewed. For cases with smaller discrepancies, preference was given to the Leukemia Registry date. A diagnostic certainty code was assigned to each case on the basis of the Leukemia Registry certainty code or noncomputerized information when such records could be found. A total of 51 cases were rejected as a result of the case review, leaving 737 cases for further consideration. Tumor registry data and coding rules *(22)* were used to assign a sequence number to each case.

Table AIV compares the Leukemia Registry and tumor registry data by period. Agreement between the two registries is excellent from 1958 through 1980, whereas the Leukemia Registry is the primary source of cases before 1958, and the tumor registries are more important after 1980.

Table I in the main text summarizes the results of the diagnostic review and case selection. Table AV provides information on the use of the Leukemia Registry–FAB in the final leukemia diagnoses by subtype for the 231 cases with DS86 estimates between 0 and 4 Gy that were used in the main analyses. There is no significant difference between the cities with respect to the proportion of cases with new diagnoses, nor are there significant differences for any subtype. Seventeen of the cases without Leukemia Registry–FAB diagnoses were Nagasaki cases (5 AML, 1 ALL, 10 ATL, and 1 other type).

APPENDIX 2

Fitted Models

This appendix contains the final fitted models for the major analyses described in this paper. The following notation is used: *t*, time since exposure; *a*, attained age; *g*, age at exposure: *s*, sex; *d*, weighted dose in sieverts.

As indicated in the expressions below, time since exposure or, where appropriate, its logarithm is centered at 25 years after exposure. Similarly, attained age is centered at 50 years. Thus the leading term in the background-rate models refers to the risk for a 50-year-old, whereas the leading term in the excess-risk models is an estimate of the risk coefficient in August 1970, i.e., 25 years after exposure. When age at exposure is used as a continuous variable it is centered at age 25. In these cases the leading coefficient describes the risk in 1970 for a person who was 25 years old in 1945. Secular trends in background rate models are written in terms of (g – 25); this is possible because all members of the cohort were exposed at (essentially) the same time. Thus the age at exposure covariate is equivalent to 1970 minus the year of birth.

Background rates are per 10^4PY, whereas the units for the EAR estimates are given in terms of excess cases per 10^4PY Sv.

Leukemia: All Types

Background rate

$$\lambda(s,a,g) = \begin{cases} 0.91e^{-0.0022(g-25)+3.08\ln(a/50)+1.22\ln^2(a/50)} & \text{male} \\ 0.45e^{-0.0022(g-25)+3.08\ln(a/50)+1.22\ln^2(a/50)} & \text{female} \end{cases}$$

Excess risk

$$\rho(d)\varepsilon(g,t,s) = \begin{cases} 0.33\left(d+0.79d^2\right)e^{-0.017(t-25)} & \text{males} \quad \text{age ATB } 0\text{–}19 \\ 0.66\left(d+0.79d^2\right)e^{-0.007(t-25)} & \text{females} \quad \text{age ATB } 0\text{–}19 \\ 0.48\left(d+0.79d^2\right)e^{-0.013(t-25)} & \text{males} \quad \text{age ATB } 20\text{–}39 \\ 0.97\left(d+0.79d^2\right)e^{-0.003(t-25)} & \text{females} \quad \text{age ATB } 20\text{–}39 \\ 1.31\left(d+0.79d^2\right)e^{-0.007(t-25)} & \text{males} \quad \text{age ATB } \geq 40 \\ 2.64\left(d+0.79d^2\right)e^{0.003(t-25)} & \text{males} \quad \text{age ATB } \geq 40 \end{cases}$$

Acute Lymphocytic Leukemia

Background rate

$$\lambda(c, s, a, e) = 0.07e^{1.34 \ln(a/50)}$$

Excess risk

$$\varepsilon(e, t) = \begin{cases} 0.21de^{-0.05(g-25)-0.14(t-25)} & \text{males} \\ 0.09de^{-0.05(g-25)-0.14(t-25)} & \text{females} \end{cases}$$

Acute Myelogenous Leukemia

Background rate

$$\lambda(c,s,a,g) = \begin{cases} 0.41e^{-0.032(g-25)+5.15\ln(a/50)-0.73\ln^2(a/50)} & \text{males} \\ 0.45e^{-0.032(g-25)+2.76\ln(a/50)-1.50\ln^2(a/50)} & \text{females} \end{cases}$$

Excess risk

$$\varepsilon(e,t) = \begin{cases} 0.15\left(d+2.25d^2\right)e^{-1.1\ln(t/25)} & g < 20 \\ 0.23\left(d+2.25d^2\right)e^{-0.04\ln(t/25)} & 20 \le g < 40 \\ 0.89\left(d+2.25d^2\right)e^{0.49\ln(t/25)} & g \ge 40 \end{cases}$$

Chronic Myelogenous Leukemia

Background rate

$$\lambda(c,s,a) = \begin{cases} 0.23e^{2.26\ln(a/50)} & \text{Hiroshima males} \\ 0.08e^{2.26\ln(a/50)} & \text{Nagasaki males} \\ 0.12e^{2.26\ln(a/50)} & \text{Hiroshima females} \\ 0.04e^{2.26\ln(a/50)} & \text{Nagasaki females} \end{cases}$$

Excess risk

$$\varepsilon(c,t) = \begin{cases} 0.17de^{-0.21(t-25)} & \text{Hiroshima males} \\ 0.005de^{-0.21(t-25)} & \text{Nagasaki males} \\ 0.70de^{-0.03(t-25)} & \text{Hiroshima females} \\ 0.20de^{-0.03(t-25)} & \text{Nagasaki females} \end{cases}$$

Other Leukemias—Hiroshima

Background rate

$$\lambda(c, s, a) = \begin{cases} 0.12 & \text{males} \\ 0.025 & \text{females} \end{cases}$$

Excess risk

$$\varepsilon(s, t) = \begin{cases} 0 & \text{males} \\ 0.44 & \text{females} \end{cases}$$

Other Leukemias—Nagasaki (ATL)

Background rate

$$\lambda(a) = 0.30e^{2.75\ln(a/50)}$$

Excess risk

None

Lymphoma

Background rate

$$\lambda(s, a, g) = \begin{cases} 0.912e^{0.028(g-25)+3.9\ln(a/50)} & \text{males} \\ 0.56e^{0.028(g-25)+3.9\ln(a/50)} & \text{females} \end{cases}$$

Excess risk

$$\varepsilon(s, t) = \begin{cases} 0.56 & \text{males} \\ 0 & \text{females} \end{cases}$$

Multiple Myeloma

Background rate

$$\lambda(a, g) = 0.11e^{0.06(g-25)+8.1\ln(a/50)}$$

Excess risk

None

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