A research paper published in the journal *Radiation Research*


*Radiation Research* 2013 (March); 179(3):361–82 (doi: 10.1667/RR2892.1)

**[Study Findings]**

This report represents a 14-year update of findings on radiation risks for cancer-like diseases of the blood and lymphatic systems and provides unique data regarding several questions:

**What are the cumulative risks of these cancers since the atomic bombings?** The data show a total excess of 94 leukemia cases associated with radiation exposure among the 113,011 Life Span Study (LSS) members. There was no excess of Hodgkin lymphoma (HL), and a marginal excess of non-Hodgkin lymphoma (NHL) among males but none among females. There was no clear excess of multiple myeloma (MM).

**How large is the risk at low doses?** There was a dose response with upward curvature for the radiation-related group of leukemia sub-types, which implies there is less risk per mGy unit of dose at low dose levels than at higher ones. In addition, risks varied markedly by time since exposure, age at exposure, and leukemia sub-type.

**Has the excess leukemia risk disappeared by this many years after the bombings?** Although the excess risks generally declined with increasing age or time since exposure, there was evidence that the radiation-associated excess risks, especially for acute myeloid leukemia (AML), have persisted throughout the follow-up period, though the excess risks are low by 55 years after the bombings.

**[Explanation]**

Leukemia and other cancer-like diseases of the blood and blood-forming organs are typically studied together and considered to be different in various aspects from other, i.e., “solid” cancers. The diseases grouped here with leukemia include cancers of the lymphoid system (lymphomas) and MM, a cancer of white blood cells called plasma cells.

After exposure to ionizing radiation such as that from the A-bombs, the risk of leukemia increases sooner than that of the solid cancers, and leukemia was the first and most striking late effect of radiation exposure seen among the Hiroshima and Nagasaki atomic bomb survivors. Leukemia also has a very high relative risk per unit radiation dose, compared to most solid cancers.

Leukemia has a number of sub-types, most of which are considered to be associated with radiation exposure but some not. Even among the radiation-associated sub-types, in addition to analyzing them as a group, there is an interest in analyzing their radiation risks separately to see how they differ. Lymphoma is also not a single disease, having the two major classifications HL and NHL.

Because a number of years had passed since the last comprehensive RERF study of the incidence of leukemia, lymphoma, and multiple myeloma, there was a need for an update. This was a considerable undertaking due to concerns about changes that had occurred in the
Objective of the study
The objective of this study was to provide comprehensive, updated risk estimates for the incidence of leukemia, lymphoma, and multiple myeloma (MM) in relation to A-bomb radiation dose.

Study methods
Incident cases were ascertained and assembled from the Leukemia Registry and the Hiroshima and Nagasaki Tumor Registries using a series of rules to give precedence to the better information when there were discrepancies, providing incidence data on 113,011 LSS cohort members with 3.6 million person-years of follow-up from late in 1950 through the end of 2001. Risk estimates were made using Poisson regression on highly stratified tables of these data to characterize the shape of the radiation dose-response relationship and, to the extent the data allowed, to investigate variation in the excess risks with gender, attained age, exposure age, and time since exposure. Both excess absolute rate (EAR) and excess relative risk (ERR) models were considered. (The ERR is based on the assumption that radiation-related risk is proportional to the baseline [zero dose] risk, which typically may vary by age, sex, and other factors, while the EAR assumes that the radiation-related risk does not depend on the level of the baseline risk.)

Results
(1) A total of 1,215 hematological malignancies were identified among LSS cohort members, 944 of which were eligible for inclusion in the analyses between 1950 and the end of 2001. Almost 40% of the eligible cases were diagnosed after the end of the follow-up (1987) used in the last comprehensive analyses of the LSS data. About 40% of the cases were leukemias, another 40% were identified as NHL, and almost 15% were MM. HL was uncommon. Almost half of the leukemia cases were classified as AML, 20% were chronic myeloid leukemia (CML), and about 12% were acute lymphoblastic leukemia (ALL). As with other populations in Japan, the incidence of chronic lymphocytic leukemia (CLL) was remarkably low.

(2) For the “radiation related” group of leukemia sub-types consisting of AML, ALL, and CML, allowing for attained age and time since exposure effects in the model, a concave upward linear-quadratic (LQ) model that contains a term for dose and a term for dose-squared described the data significantly better than either a linear dose response or pure quadratic dose-response model (Figure). The estimated linear dose effect in the LQ ERR model at attained age 70 after exposure at age 30 was 0.79 (i.e., a 79% excess) at 1 Gy and the estimated curvature was 1.2, which means that the risk coefficient for the square of dose was 1.2 times the coefficient for the linear dose effect. For example, the total ERR at 1 Gy was $0.79 \times (1 + 1.2 \times 1^2) = 0.79 \times 2.2 = 1.74$, whereas the ERR at 0.01 Gy would be $0.79 \times (0.01 + 1.2 \times 0.01^2) = 0.79 \times 0.01012$, which is very close to $0.79/100$—the dose-squared term contributes almost nothing. Thus the estimated risk at lower doses is substantially less than it would be for a purely linear dose response with the same total ERR of 1.74 at 1 Gy. It was estimated that about 94 of the 312 cases of AML/ALL/CML leukemia used in these analyses were associated with the radiation exposure.

a. For AML analyzed separately (176 cases), a pure-quadratic model with an
estimated ERR at 1 Gy of 1.11 (standardized to age 70 after exposure at age 30) described the data as well as a linear-quadratic model.
b. For NHL (402 of 437 lymphoma cases), while there was some evidence of a statistically significant radiation effect in men, there was no indication of a radiation effect in women.

(3) There was no evidence of radiation-associated excess risk for HL or MM.

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

The Radiation Effects Research Foundation has studied A-bomb survivors in Hiroshima and Nagasaki for more than 60 years. RERF’s research achievements are considered the principal scientific basis for radiation risk assessment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and for recommendations regarding radiation protection standards by the International Commission on Radiological Protection (ICRP).

*Radiation Research,* which is an official monthly journal of the U.S. Radiation Research Society, publishes original papers and review articles on radiation effects and related issues in the fields of physics, chemistry, biology, and medicine. (Impact factor in 2011: 2.684)