

II. BIOLOGICAL EFFECTS

D. Leukemia and Related Disorders

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The studies of radiation leukemogenesis in atomic bomb survivors is reviewed. Leukemia appeared early and was one of the most striking evident somatic effects of radiation in atomic bomb survivors. Leukemogenic effects of radiation vary by quality and quantity of radiation dose, age at the time of exposure, elapsed time after exposure and type of leukemia. Although the risk of leukemia in atomic bomb survivors is now greatly reduced with elapsed time after exposure, there is no evidence that the risk of leukemia has returned to control levels in those survivors who received a significant radiation dose even almost 30 years after the bombings. No significant clinical and pathologic manifestation of leukemia related to radiation dose was reported except the absence of chronic lymphocytic leukemia in those survivors who received a significant dose. A briefer review is also made of various studies concerning atomic bomb exposure and the incidence of related disorders such as malignant lymphoma, aplastic anemia and other hematologic disorders.

LEUKEMIA

The leukemogenic effect of ionizing radiation in man has been demonstrated by the experience of the atomic bomb survivors in Hiroshima and Nagasaki, in patients with ankylosing spondylitis in Great Britain treated by X-rays, and by mortality studies of radiologists.

Over the past 25 years, American and Japanese scientists at the Atomic Bomb Casualty Commission (ABCC) and the Hiroshima and Nagasaki medical schools have reported on the incidence of leukemia as a late effect of atomic radiation.¹⁻⁷⁾ With the advantage of improved dosimetry for both gamma and neutron radiation in the fixed sample of survivors in Hiroshima and Nagasaki,⁸⁻¹⁰⁾ these investigators have been able to investigate the relationship between radiation dose and the incidence of leukemia. On the linear hypothesis, now questioned, and without regard to type of leukemia or quality of radiation, the apparent excess incidence in A-bomb survivors is about 1.8 cases per million person-year rads for the period 1950-1970.¹¹⁾ Using the confirmed cases of leukemia occurring from 1950 to 1966 in the fixed cohort of atomic bomb survivors and controls, Ishimaru et al.⁵⁾ found that the risk of leukemia in Hiroshima was significantly elevated even in those exposed to less than 50 rads. In the smaller Nagasaki series, however, a significant increase in risk could not be demonstrated among those exposed

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to low doses. The inter-city difference in dose response appeared to be due to the high Relative Biological Effectiveness (RBE) of neutrons compared with gamma rays; for leukemia, RBE is about five, on the average, and the neutron component is quite small in the Nagasaki dose.

In view of the scientific and practical importance of establishing the probable functional form of the dose-response curve for gamma radiation, and the suggestion that the dose-response curve for the Nagasaki (gamma) data is non-linear, the BEIR Committee¹³⁾ suggested that it would be desirable to confirm this finding by analyzing all the data of the Hiroshima and Nagasaki Leukemia Registries, not merely that portion which falls within the Atomic Bomb Casualty Commission-Japanese National Institute of Health (ABCC-JNIH) fixed cohort. However, there are problems associated with the use of all leukemia registry data in this way, especially the difficulty of estimating the dose distribution of the A-bomb survivors in the two cities over the entire period since 1945, or 1950. Only for 1950 is a reasonably accurate dose estimate available. This is because the migrants to and from Hiroshima and Nagasaki have not been systematically interviewed as to location at the time of the bomb and shielding information, ABCC studies having been based on fixed cohorts selected from among those in Hiroshima or Nagasaki City as of 1 October 1950.

Although the number of Nagasaki cases in the low dose region is small, attempts have been made to estimate a single parametric dose response function covering both cities. Several recent analyses¹⁴⁻¹⁷⁾ of the Hiroshima and Nagasaki data for all forms of leukemia combined suggest that an appropriate dose-response function is linear for the neutron dose and quadratic for the gamma dose. Figure 1 shows the crude annual incidence rate of leukemia (all types) in the ABCC-JNIH fixed cohort during Oct. 1950-Dec. 1971 by city and dose categories. It appears that the risk was greater in Hiroshima than in Nagasaki in every dose category, except less than 50 rads, although the risk increased with dose in both Hiroshima and Nagasaki. The dose response curve also differs by type of leukemia. The risk of acute leukemia significantly increases in those who received 100 rad or more. The risk of chronic granulocytic leukemia increases in the low dose as well as in the high dose region.

Although the annual incidence of leukemia among the survivors who were heavily

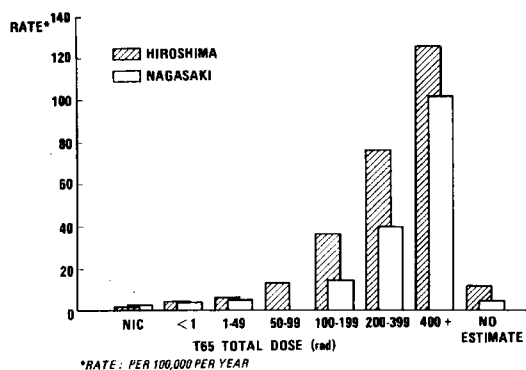


Fig. 1. Crude annual incidence rate of leukemia (all forms) in the extended Life Span Study sample by city and dose, October 1950-December 1971.

exposed to the atomic bomb radiation has declined markedly since the peak was reached in 1951-1952, the evidence indicates that the risk of leukemia among survivors exposed to high doses had not yet returned to normal even 20-25 years after exposure.^{11,18)} From the most recent analysis of data on the fixed cohort (109,000 subjects) of atomic bomb survivors and controls, annual numbers of confirmed leukemia cases are shown in Figure 2 by dose and type of leukemia.

No chronic lymphocytic leukemia has developed in survivors who received 1 rad

or more in either Hiroshima or Nagasaki.^{5,18,19,20}) This is true for both the fixed cohort and the whole Hiroshima and Nagasaki Leukemia Registry data over the years, although 10 cases of chronic lymphocytic leukemia were detected among survivors in Nagasaki who had received less than 1 rad. The ankylosing spondylitis patients who were treated by X-ray irradiation also showed no increased risk of chronic lymphocytic leukemia;²¹⁾ only one case was reported during 24 years' follow-up study. The exception that chronic lymphocytic leukemia was not induced by radiation is of particular interest from the standpoint of a general theory of radiation carcinogenesis.

The dose response relationship differs by type of leukemia.^{5,18)} The risk of chronic granulocytic leukemia is significantly increased for Hiroshima survivors in the low dose region, but no such increase can be observed in the Nagasaki survivors. The risk of acute leukemia is elevated for those who received 100 rads or more in each city.

Jablon and Kato¹¹⁾ reported that those who were in either the youngest or oldest age brackets at the time of exposure were more sensitive to the leukemogenic effects of radiation, while those in the intermediate age range (10-49) had a substantially lower risk. The evidence¹⁸⁾ of the Leukemia Registry is that the younger the age at the time of bombing (ATB), the greater the risk of contracting leukemia during the early period, and the more rapid the decline thereafter. On the other hand, in the group aged 45 or more ATB, the increase in risk occurred later and persisted during the period 1960-1971. Acute forms of leukemia contributed to these trends. The risk of chronic granulocytic leukemia among survivors exposed to large doses was the greatest 5-10 years after exposure and subsequently decreased regardless of age ATB. Although the influence of age ATB, calendar time, and radiation dose on the incidence of leukemia is fairly complex, it can be shown by means of a schematic diagram as in Figure 3.

Studies of leukemia in the Hiroshima and Nagasaki City populations of A-bomb survivors have yielded findings generally similar to those derived from studies of the fixed cohort. Ichimaru²²⁾ reported that the average age ATB among the proximally exposed Nagasaki leukemia cases in the city population tends to increase with time after exposure. Takahashi et al.²³⁾ reported that it was only in the survivors who were exposed

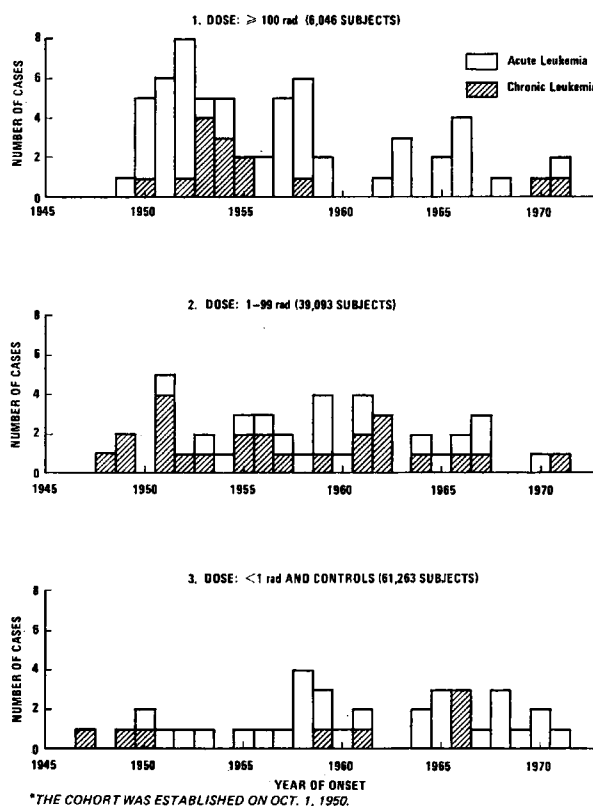


Fig. 2. Distribution of definite and probable leukemia in the fixed cohort of atomic bomb survivors and controls, Hiroshima and Nagasaki, by year of onset, dose and chronicity of leukemia

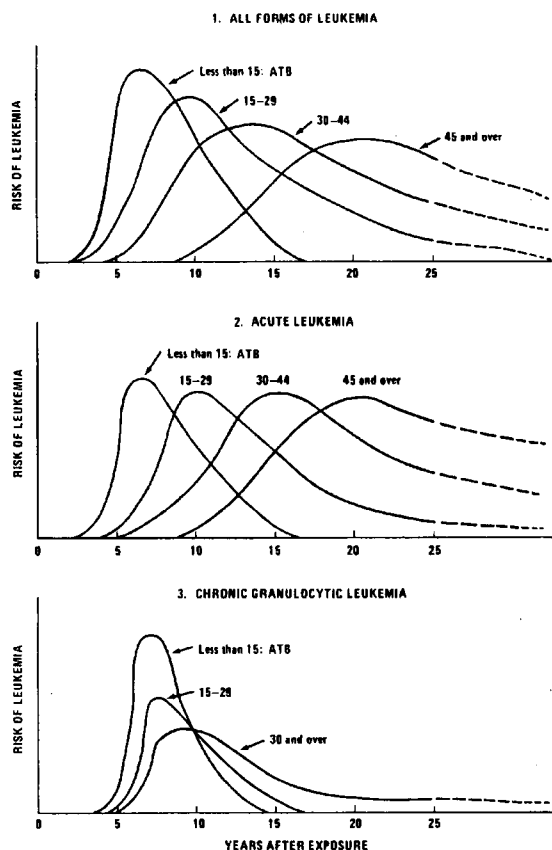


Fig. 3. Schematic model of influence of age at time of bombing (ATB) and calendar time on leukemogenic effect of radiation (heavily exposed survivors)

In general, the clinical manifestations of leukemia are similar in proximally and distally exposed cases of the same type and age; chronic granulocytic leukemia, however, was more prevalent in the low dose than in the high dose survivors in Hiroshima. Bizzozero et al.³²⁾ reported median survival times by type of leukemia and distance from hypocenter. Survival time did not appear to differ between the proximal and distal exposed. In their study of autopsy material, Liu et al. found significantly longer survival times in chronic granulocytic leukemia patients who received 1 rad or more than in those received less than 1 rad or who were not in city ATB. However, since no further dose response relationship could be demonstrated, they concluded that factors other than radiation were responsible. Yoshimura et al.³³⁾ recently analysed survival data for 1,561 cases in the Leukemia Registry in relation to dose, type, and year of onset. They found no significant dose-survival rate relationships in relation to type of leukemia, sex, age, and year of onset.

The frequency of the Ph 1 (Philadelphia chromosome) seen in patients with chronic granulocytic leukemia has been found not to differ between survivors and controls.³⁴⁾

In their pathological study of leukemia from atomic bomb survivors for the time period 1949-1969, Liu et al. examined the weights of spleen, liver and kidney, the severity of tissue infiltration by leukemic cells in each organ, degrees of bone marrow

within 2.0 km from the hypocenter and whose age ATB was 20-59 that the risk of leukemia remained elevated after 1960 in Hiroshima.

Arakawa²⁴⁾ and Hashizume et al.²⁵⁾ have estimated that radiation doses were very low for those survivors who were exposed to only isotopic radiation from fallout. Two confirmed cases of chronic granulocytic leukemia were found in 1960 and 1970 among the residents of the Nishiyama district in Nagasaki^{7,26)} where Arakawa estimated that exposure was limited to radioactive fallout. However, no conclusion can be drawn as to the role of radiation in the etiology of these two cases of chronic granulocytic leukemia.

Although Stewart and Kneale³¹⁾ reported that the risk of leukemia increased linearly with number of medical X-rays received during gestation, no such increase in leukemia has been seen in the in-utero exposed.²⁷⁾ No increase in risk of leukemia has been seen in the survivors' children conceived after the bomb.²⁸⁻³⁰⁾

and splenic fibrosis, frequencies of active and inactive tuberculosis, and frequencies of chloroma in patients with myelogenous leukemia, all in relation to exposure doses. No significant differences were noted in these parameters between those who received a significantly high radiation dose and those who did not, except for a less intense infiltration of leukemic cells into the lungs of chronic granulocytic leukemia patients.

At least one attempt has been made to study epidemiologic factors other than exposure to the atomic bombs. Ishimaru et al.³⁸⁾ found that leukemia is associated with occupational exposure to medical X-rays and to benzene derivatives, but that no association was seen with other factors, e. g., socio-economic status, dog bite, exposure to pets, etc. Further study is required with respect to possible additive effects of two factors, A-bomb exposure and occupational hazards (benzenes and X-ray).

RELATED DISORDERS

A study of cases occurring through 1965 showed that malignant lymphoma increased in Hiroshima survivors exposed to 100 rads or more (25.5 per 10,000 sample during 15 years), but not in their Nagasaki counterparts.³⁹⁾ If not a chance occurrence, this discrepancy may be due to differences of types of radiations between the two cities. At present, the lymphoma data supplemented by cases added through 1972 are being analyzed in order to resolve this question.⁴⁰⁾

So far, only one case of multiple myeloma has been detected among the survivors in the Hiroshima Life Span Study (LSS) sample who received 100 rads or more.³⁹⁾

Ichimaru et al.⁴¹⁾ estimated that the relative risk of aplastic anemia in the survivors with 1 rad or more to be 1.8 times higher than those with less than 1 rad during the time interval from 1950 to 1967. However, this increase was not statistically significant. Aplastic anemia among A-bomb survivors did not differ clinically or pathologically from the same disease seen in the general population.⁴²⁻⁴³⁾ From their analysis of death certificate for the period 1950-1966, Beebe et al.⁴⁴⁾ reported evidence suggestive of increased mortality from diseases of the blood and blood-forming organs in heavily irradiated survivors. Plans are being made to re-examine the incidence of aplastic anemia in atomic bomb survivors based on data through 1974.

Over the years, a number of reports⁴⁵⁻⁵¹⁾ have been published concerning the status of various hematological disorders in the survivors (see also the paper by Ohkita in this issue). The finding of an increased frequency of chromosome aberrations in cultured lymphocytes from the heavily exposed survivors and children exposed in *utero* has been reported elsewhere⁵²⁻⁵³⁾ (see also the report by Awa, this issue, on somatic cell chromosome aberrations).

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