Recent Evidence of Radiation-Induced Cancer

in the Japanese Atomic-Bomb Survivors

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Abstract

The prospective study of survivors of the atomic bombing of Hiroshima and Nagasaki utilizes as a control population those persons who were far enough from the detonation to receive no exposure, but who were in the cities at the time of the bombing (ATB). Radiation exposure data are still being revised; the new evaluation indicates that the results from the two cities can be combined, since fast neutron exposures were low and were similar in both cities. New tissue doses are about half those presented previously. Many confounding factors affecting cancer rates have also been evaluated, such as medical radiation, smoking, childbearing, diet and indoor radon. The most recent follow-up data support the following conclusions: (a) the dose-response relationship is consistent with a straight line throught the origin, including the lowest dose group (~ 3 rad); (b) sensitivity to induction of cancer varies considerably by tissue irradiated; (c) most cancers show a radiation effect still increasing 40 years after exposure; (d) a small leukemia excess among those irradiated is still present in Hiroshima; (e) the thyroid cancer excess is declining at this time; (f) smoking adds to the effect of radiation on lung cancer incidence; (g) certain benign tumors show a radiation-related effect; (h) children

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under the age of 10 ATB are presently showing the highest relative risk for cancer compared to all other ages ATB at equal attained age. If this last effect continues to persist, then age-specific lifetime cancer risk coefficients will be necessary, and for those irradiated as young children may be quite high.

The follow-up studies of survivors of the atomic bombing in Hiroshima and Nagasaki have now extended for 40 years, the largest prospective human epidemiologic study yet undertaken. In defining the effects of low doses of ionizing radiation, the A-bomb survivor study is especially important because it involves a group of people of all ages and both sexes who were in reasonable health prior to radiation exposure. Among the survivors identified in 1950 and who are included in the study population the average tissue dose for those exposed to 1 rad or more is about 20 rad, and thus many results are especially relevant to effects of low doses of radiation, contrary to the usual view that the A-bomb findings are primarily related to high doses.

Until recently it was thought that the type of radiation exposure in the two cities differed significantly, in that the Hiroshima uranium-235 bomb was believed to have a much higher proportion of high energy neutron exposure at ground level than the Nagasaki plutonium-239 bomb. The most recent reassessment of dosimetry (1,2), however, has indicated that the distribution of high energy neutrons by distance from ground zero was very nearly the same in both cities. Although the free-in-air gamma ray doses continue to be proportionately somewhat higher in Nagasaki compared to Hiroshima at equivalent distances, the neutron component in both cities is now too small to provide any conclusive basis for ascribing differences between results in each city to the quality of radiation exposure.

In addition the shielding of gamma rays by houses and other buildings, in which most of the survivors were present at the time of exposure, was formerly underestimated; the new dosimetry system leads to a reduction of doses (about 2 fold) because of the reduction of neutron dose and the greater shielding of gamma rays. With this system applied, the dose-response relationship for radiation—induced cancer is very similar in the two cities (within about 3%). The results for both cities can be combined, therefore, with an improvement in the statistical reliability of the resulting cancer risk estimates.

The population under study at the Radiation Effects Research Foundation (RERF) for assessment of long-term effects of ionizing radiation is the Life Span Study (LSS) sample; follow-up of this sample began in October 1950. The LSS sample consists of persons who were living in either Hiroshima or Nagasaki at the time of the census of A-bomb survivors conducted by the Japanese government in 1950. As originally defined, the sample included (1) most persons alive at that time who were within 2,500 m from ground zero in either city at the time of the bomb (ATB), (2) a sample of persons who were between 2,500 and 10,000 m from ground zero ATB, and (3) a sample of persons who were not in city (NIC) or beyond 10,000 m. The latter two samples were obtained by matching by sex and age to a group of survivors who were less than 2,000 m from ground zero in each city. The original sample has been extended, most recently in 1982 by the addition of approximately 11,400 distally exposed (2,500-10,000 m) Nagasaki residents for whom complete follow-up data are available. As currently defined and with the NIC group eliminated, the total study population is presently 93,614 (61,911 in Hiroshima and 31,703 in Nagasaki); about one-third have died in the period 1950 to 1982. Analysis of the data has used those who were about 3,000 m or more from ground zero (and thus whose doses were less than 0.5 rad) as the control (non-exposed) population.

An important subset of the LSS is the Adult Health Study (AHS) population, which has had extensive and continuing clinical evaluations beginning in 1958. This group was selected to include a high proportion of individuals exposed to high doses, and a random sample of survivors with lower doses. In 1958 a total of 19,962 persons were selected from the entire LSS population, as it was then defined. Of these, 16,738 had been examined at least once by the end of 1978. In 1977, another 2,436 persons were added to the AHS population, and over 60% of these were examined at least once within four years. All AHS subjects living in or near either city are encouraged to return every two years for detailed evaluation of their health status, including medical history, physical examination, laboratory evaluations, and special clinical studies as needed. This population has been useful in detecting radiation dose-related effects on the prevalence of benign tumors.

Mortality data within the LSS sample are obtained by periodic checks of the Japanese system of local family registration offices (Honseki). These offices maintain records of family vital events, births, marriages, deaths, etc., and each living sample member's record (Koseki) is periodically reviewed to determine vital status. Whenever a record of a person's death is found, the date and cause of death are obtained from the vital statistics death schedule at the Health Center for the place of death; the cause of death reported by these centers is obtained from death certificates. Because of the comprehensive nature of the Koseki system, ascertainment of death is believed to be virtually complete for subjects resident in Japan. The hazards of relying on death certificates to establish the primary cause of death are well known. A comparison of certified cause of death and autopsy diagnoses (3) revealed that cancer confirmation and detection rates vary widely according to the type of cancer. The accuracy of death certificates in the LSS population was found to be high for malignant neoplasms of some organs such as breast and stomach, and for leukemia. But for others, such as lung, urinary tract, liver and biliary system, pancreas, and prostate, death certificate data were found to underestimate the presence of cancer considerably (4). This underestimation will produce an equivalent underestimation of the absolute excess risks associated with exposure to radiation.

Information on cancer incidence is also obtained through the tumor registries established in both cities by the local medical societies in the late 1950s, tissue registries in each city, and supplementary case finding efforts conducted for particular studies. At this time reporting of cases by the tumor registries is considered to be good for the two cities. The registries incorporate cases only for those resident in each city at the time of the diagnosis, thus there is underascertainment of cases in the LSS population because of migration out of the cities, a particular problem for those who were young ATB. Data from the AHS population indicate that since 1958 out-migration has been slight (only a few percent). However, prior to that time about 10% of all those living had left. As many as 20% of the members of the youngest age ATB groups may have left the cities prior to 1958. Tokunaga et al. (5) cited evidence that among AHS females the migration rate was unrelated to radiation dose. Because most of those leaving have settled in the large cities of Honshu and Kyushu, it is possible that they could be traced to tumor registries there, in order to bring the ascertainment of incident cancer closer to 100%.

The cancer incidence data have the advantage that cases are included in the study at the time of diagnosis, often years before fatal cancer would be found from death certificate records. Not only may there be a substantial lag between diagnosis and death, but sometimes as much as two years may elapse before the death certificate data are recorded and detected from the Koseki. The delay in ascertainment from death records is especially important because cancer cases in the LSS are rapidly accumulating, and the evidence of radiation dose-related effects is increasing.

Another important factor in use of tumor registry data is the fact that cases are recorded regardless of outcome. Thus information on non-fatal malignancies and some types of benign tumors can be obtained from the registries. This issue is especially significant for cancer of the thyroid and female breast, which are radiosensitive but not highly fatal. The radiosensitivity of cancer of the prostate is uncertain, in part because ascertainment of cases of cancer of the prostate from death certificates is poor in Japan. Data from the tumor registries, for which ascertainment is somewhat better, indicate a radiation dose-related effect (6). Finally, it should be emphasized that use of incident cancer as a basis of defining cancer risks gives an indication of radiation effects that is generally more meaningful in terms of total social cost than simply cancer deaths alone. Incident cases are not yet completely analyzed for the period up to 1982, and therefore the main emphasis in this report will be on mortality evaluation.

Host and environmental characteristics such as smoking habits, diet, socioeconomic status, childbearing history, occupation, and many other details have been collected in a series of interview and mail surveys of large subsets of the LSS sample conducted at various times between 1963 and 1981. These data have been useful in efforts to deal with factors other than A-bomb radiation exposure which might affect cancer risks. An important potential confounding factor is exposure of the study population to medical X-rays. Evaluation of this source of additional radiation exposure could be important in future analyses of LSS data, particularly for those subjects given X-ray therapy for benign conditions. A survey of hospitals in the Hiroshima area, as well as among the AHS population, indicates that average cumulative radiation exposure to the bone marrow or gonads since 1945 has been less than 2 rad from diagnostic X-ray (7). With regard to therapeutic radiation, local doses in excess of 1,000 rad have been received by approximately 2,000 persons in the LSS (8). About 65% of this therapy has been for cancer, therefore among this group the primary interest is in the possibility of second primary malignancies.

Recent Results

A preliminary analysis of follow-up of mortality through 1982 has been carried out using the most recent estimates of revised dose data available in 1986. Figure 1 shows the dose-response for all malignant neoplasms except leukemia, 1955-1982, with results for both cities combined. Risk relative to the zero dose group is plotted against mean tissue dose. In calculating the dose a quality factor of 10 for the neutron component has been applied, and tissue doses have been calculated assuming a constant value of 0.7 for tissue transmission (9). Grouping by dose categories has been on the basis of the old dosimetry, corrected for the new changes at each level, but there will be some reassignment of individuals on the basis of the new dosimetry. Thus these results may be modified somewhat by further analysis. The period from 1950 to 1954 has been excluded because except for leukemia the person-years 5-10 years from the exposure are at low risk from radiation-induced cancers due to the minimum latent period required for the development of the solid cancers.

A number of points may be made from Figure 1. First, for the four lower doses, at least, the relationship is reasonably close to a straight line down to and including the dose at 3 rem. At higher doses there is evidence that people may have been misclassified by dose; these were people in whom shielding by building construction or materials may have determined their survival, and for whom shielding estimation is less accurate. If an equation of the form $E = aD + bD^2$ is used to fit the data points, where E is the excess relative cancer risk, D is dose, and a and b are constants, the coefficient b is found to be negative. In other words, the best fit of the equation in this case is curvilinear downward, implying greater effect per unit dose at low doses than at high doses. The two lowest dose points, at 3 and 16 rem, have 2606 out of 3383 cases observed, or 77% of all cancer deaths among those observed in all groups exposed to 1 rem or more. Moreover these groups, exposed at greater distance from ground zero, have more reliable dosimetry, which is less sensitive to errors of location and shielding, than the groups exposed to higher doses. As of 1982, the lowest dose group shows a 3.26% excess relative risk of cancer for a mean tissue dose of about 3 rem, or a doubling dose for all cancers except leukemia (dose required to double the cancer mortality) of 92 rem. For the second data point the excess relative risk is 9.14% for a mean tissue dose of about 16 rems or a doubling dose of about 175 rem. If we pool the results from these two data points, with a combined average dose (weighted) of about 7.4 rem, the doubling dose is about 138 rem. For the pooled results for the remaining five higher dose categories, with a weighted mean dose of 94.0 rem (777 total cancer deaths observed), the doubling dose is about 315 rem. The lower doubling dose at the low doses is an expression of the downward curvature of the cancer risk dose-response derived from these data.

When one looks at individual sites of cancer among the A-bomb survivors, the radiation dose-related excess risk relative to the zero dose group is quite variable, indicating that some types of cancer may be more easily induced by radiation than others. Some of this variability in the cancer mortality results may depend on inaccuracies of death certification, especially a problem in Japan for cancers of the prostate, uterine cervix, pancreas and liver and biliary system (4). For example deaths certified to prostate or pancreatic cancers show no relationship with radiation dose, up to 1982, but a positive dose-response relationship has been demonstrated for prostatic and pancreatic cancers obtained from the tumor registries. Despite these questions it is evident that thyroid cancer (incidence), leukemia, cancer of the female breast, urinary tract cancer, lung cancer and multiple myeloma are among the most sensitive to radiation in the A-bomb survivors. One should note that the ability to detect these effects in the LSS sample depends on the cancer frequency; for cancers diagnosed rarely in Japanese, such as bone cancer or Hodgkin's disease, no radiation effect may be detectable because the numbers observed are too small.

Figure 2 shows the dose-response for leukemia deaths in the LSS sample for the period 1950 to 1982. There are only 158 deaths distributed among the seven dose categories, thus the statistical reliability of each point is much less than for the points in Fig 1. Nevertheless the dose-response apparently shows a curvilinear relationship somewhat different than is found in Fig 1, with low doses less effective per unit dose than the high doses. One should note, however, that the relative risks on the ordinate of Fig 2 are very high. If a straight line is drawn through the four lowest dose points and the origin, the doubling dose is found to be about 35 rem for all age groups combined.

Investigation of the trend of relative risk by four-year time intervals since 1950 shows that the excess risk of leukemia per rem has declined steadily since 1958, although a relative risk of about 2 (5 cases vs 2.7 expected) still was observed in the period of 1979-82 for those exposed to greater than about 20 rem tissue dose. In contrast, for all cancers except leukemia the excess relative risk per rem for the exposed population is continuing to increase during the period 1959 to 1982, and is highest for the period 1975 to 1982. Over-all there is no evidence for cancer mortality of a decline in excess relative risk up to 1982, 37 years after the exposure. For some particular cancers besides leukemia, however, a decline in risk with time appears to be present. Thyroid cancer incidence per rem is beginning to decline, and so also is multiple myeloma, although the number of cases, thirty-five, is too small to be certain.

The excess relative risk per rem of all cancers except leukemia is about twice as high in women compared to men. This sex difference is largely due to the low cancer age-specific death rates among women compared to men. In absolute terms there is little difference by sex in excess cancer mortality per rem, though it is likely to be present in analyses of cancer incidence because of the importance of breast and thyroid cancer (with high survival rates) among women. For leukemia there is no sex difference in relative risk per rem, but in absolute terms the risk is about twice as high in males.

An important finding with continuing follow-up of this population is the effect of age at exposure on subsequent cancer risk. Those survivors who were under age 10 ATB are now reaching ages when cancer is beginning to occur more frequently, and thus it is beginning to be possible to determine their excess risk at the same attained age as those who were older ATB. When this is done it is evident that the excess relative risk is generally substantially higher for those irradiated at young ages. As of 1982 the excess relative risk per rem for those children under 10 years of age ATB is about 8 times higher for all cancers except leukemia, compared to those over age 35 ATB. This difference in effects of age at exposure may decline as the cancer rates rise with older age in this youngest group, but if it is found that the higher excess relative risk in this group persists throughout their lives, then it is apparent that children are at special risk of developing cancer from radiation exposure. In the case of leukemia, for which the excess risk is now nearly completely defined for all age groups, the excess relative risk for those under age 10 ATB is about four times greater than for those over 35 ATB. With all dose categories combined, the doubling dose for leukemia is about 4 rem for children exposed under the age of 10. A similar effect of age at exposure has been demonstrated for the incidence of breast cancer in women exposed under the age of 10 (5).

With regard to the additional personal or environmental factors which could interact with the radiation-related cancer risk (confounding by other randomly-present contributors to cancer would be expected to reduce the apparent effect of radiation), most have not been found to modify the radiation effects significantly. In the case of cigarette smoking in relation to lung cancer, a case-control evaluation of lung cancer cases has indicated that the effects of smoking and radiation were nearly additive together. Thus, among women, most of whom did not smoke, the absolute excess of lung cancer related to radiation exposure was about the same as for men, most of whom did smoke. Unexposed women had a low rate of lung cancer, thus the excess relative risk from radiation exposure was much higher than for men, whose lung cancer rates were high because of smoking, among those unexposed to radiation.

The mortality analysis does not adequately detect benign tumors because they usually are not recorded as the primary cause of death. It has been possible to determine benign tumors in the AHS sample examined every 2 years in the RERF clinic. Conditions which show a dose-related effect of radiation in this population include gastric polyps, uterine fibromas and non-malignant thyroid disease (10). The possibility of a relationship of these benign conditions to subsequent development of malignant cancer at these sites is of interest.

In summary, the follow-up study of the A-bomb survivors continues to yield important results. The new evidence indicates that the risk per rem of radiation-induced cancer is higher than previously thought for the following reasons: (a) the new evaluation of radiation exposures indicates that the doses were previously overestimated, thus it is now evident that the excess cancers were produced with lower radiation doses than were thought to apply; (b) for most cancers the excess relative risk in those irradiated is continuing to increase with time of follow-up; (c) those irradiated at young ages are showing higher relative cancer risks per rem than those who were older at the time of exposure, when compared at the same attained ages. The straight line relationship between radiation dose and excess cancer risk is well-supported for all cancers except leukemia. The data suggests that at low doses the relative risk is an increase in all cancers including leukemia of about 0.75% per rem for this exposure condition, consistent with a doubling dose of 133 rem. It is likely that this relative risk coefficient will be found to depend on age at irradiation, with an excess cancer risk of 2% per rem or more for those irradiated under the age of 10. Based on these results and the normal spontaneous cancer rates in Japan (only about 60% as high as those found in Western countries), the lifetime absolute excess risk is at least 1 excess (incident) cancer case per 1000 persons exposed per rem, for all ages, and substantially higher for irradiated children.

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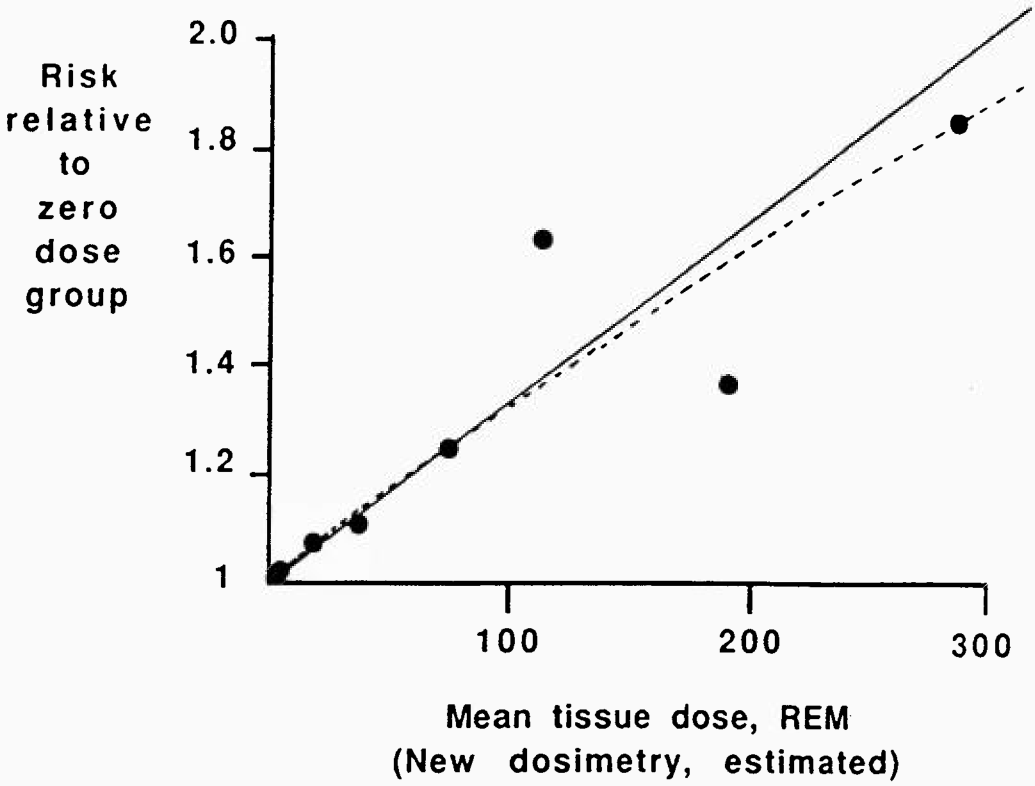
Legends for Figures

Fig 1. Cancer mortality in LSS sample plotted against mean tissue dose in rem, for all malignant cancers except leukemia. Data for the period 1955 to 1982, both cities and both sexes combined, and all ages. Ordinate: Cancer risk relative to the unexposed group. Doses estimated from new dosimetric system, with a neutron quality factor of 10 applied. Solid line: straight line fit to data drawn through origin. Dashed line: line fitted to equation: Effect $= aD + bD^2$ where D is dose and a and b are constants. The downward curvature indicates that the coefficient b is negative.

Fig 2. Leukemia deaths in LSS sample vs. mean tissue dose in rem. Data for the period 1950-1982, both cities and both sexes combined, and all ages. Ordinate and abscissa as in Fig 1. The solid line is fitted by eye.



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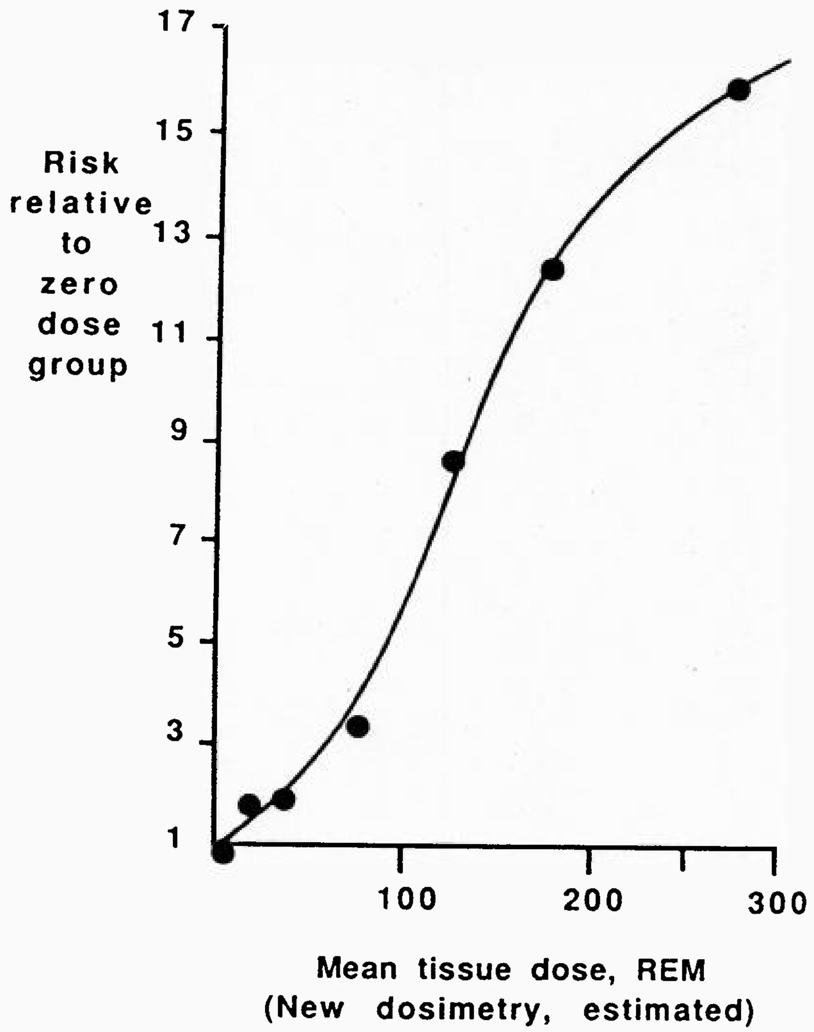

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