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DOSE-RESPONSE ANALYSES AMONG A-BOMB SURVIVORS EXPOSED TO LOW-LEVEL RADIATION

by

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Dose-response Analyses among A-bomb Survivors Exposed to Low-level Radiation

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A long term cohort follow-up study of approximately 110,000 A-bomb survivors and controls has been carried out by the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF). Among the A-bomb survivors exposed to 1 rad or more, a majority (79%) numbering 38,000 were exposed to less than 50 rads. Thus examination of the dose response for radiation effects among those exposed to low dose levels, defined here as less than 50 rads should provide a fairly good chance of detecting the phenomenon of radiation hormesis, if indeed present. However, it should be noted that it is doubtful whether any epidemiological study of cancer mortality or morbidity, or the other endpoints examined here can establish unequivocally the phenomenon of hormesis. There are too many extraneous factors affecting these endpoints which can be mitigated either through survey design or statistical analysis or both that a firm conclusion about the effects of low doses cannot be drawn from one study alone. Conceivably a persuasive case might emanate through the examination of many sets of data, and this analysis and these observations are presented in the belief that they might constitute a part of such an aggregate effort.

Materials and Methods

A re-analysis was conducted to determine the radiation dose response for subjects exposed to less than 50 rads, using a more detailed dose grouping than used in the following reports: I) Cancer mortality among Life Span Study subjects 1950-78;[1] II) Cancer incidence among Life Span Study subjects, 1959-78, based upon the Nagasaki Tumor Registry[2] (It should be noted that Dr. Lucky discussed in his paper the dose response of cancer mortality and incidence among A-bomb survivors based on the material of these two references.); III) The frequency of cells with chromosomal aberrations among Adult Health Study subjects;[3] IV) Phytohemagglutinin (PHA) response of peripheral lymphocytes

among Hiroshima Adult Health Study subjects;[4] and V) The frequency of mental retardation among children exposed in utero.[5]

Subjects of the present study were divided into the following five dose groups: 0, 1-5, 6-9, 10-19 and 20-49 rad on the basis of their estimated T65DR.[7] Relative risk (RR) based on the frequency of events in the 0 rad group and its 95% confidence limits[6] were calculated. Age and sex adjustments were routinely made in the analyses of cancer mortality and morbidity rates based on the observed person-years at risk.

Results

Cancer mortality: Although the relative risk of mortality for all cancers except leukemia (the 0 rad group was used for comparison) varied among the five dose groups, they did not differ statistically from unity ($P>0.10$). The relative risk for the 6-9 rad group in Hiroshima and for 1-5 rad group in Nagasaki were actually lower than one, but they were still within the range of random variation. For leukemia mortality, the variation in the relative risk estimates was much greater than that for all cancers except leukemia, because of the small number of deaths. In Hiroshima, the relative risk was lower than unity for both 1-5 and 6-9 rad groups, but they were still within the range of random variation. In Nagasaki, a lower relative risk (RR=0.65) for the 20-49 rad group was observed, but there was only one leukemia death. There was no case observed in the 50-99 rad group in the same cohort in contrast to a significantly higher mortality rate observed among those survivors exposed to more than 100 rad.[1]

A similar tendency was also observed when the analysis was extended to other sites of cancer, such as cancers of the lung, stomach, breast, and thyroid.

Chromosomal aberrations: The relative risk for cells with chromosomal

aberrations seemed to increase with dose and regardless of which comparison group was used, the relative risk was not less than unity.

Immune response: There have been few studies at RERF which can assess the relationship of immune response to dose, although several extensive studies are currently underway. The T-lymphocytes response to phytohemagglutinin (PHA) varied among the five comparison groups, but the difference was not statistically significant. However, the response seemed to be lower in the higher dose group.

Mental retardation among the prenatally exposed: The frequency of mental retardation increase with dose, especially for those survivors exposed from the 10th to 17th gestational week as measured from the last menstrual period, or from the 8th to 15th week after fertilization.

Discussion

The analysis so far described is based on the T65 system of dosimetry.[7] Though the T65 dose system will be revised based on the current reassessment of A-bomb dosimetry,[8,9] the final results of such activities are not yet available. At present, the preliminary results using interim dose estimates indicated a generally increasing trend with dose among the comparison groups. Such results were observed in both the T65 and the interim dose systems, though the detailed shape of the dose response and the risk coefficients differed with the system used. Thus, the current analysis, based on the total kerma dose of the T65 dose system, did not provide any unequivocal evidence on whether or not the phenomenon of radiation hormesis is present among the A-bomb survivors, but as stated earlier this was not anticipated. Needless to say, a reanalysis of these data will be made when the final revised doses become available.

In general, it is difficult to determine the effects of ionizing radiation directly among subjects exposed to low doses of radiation; huge

sample sizes are required if the estimates are to have any reasonable stability and small differences are to be detected.[10] Furthermore, extraneous sources of variation which may vary among dose groups become more important than at higher doses and at these levels of exposure the actual doses may not be as reliably ascertained as would obviously be desirable. Medical exposures could be a more serious source of extraneous variability than at higher doses. Other environmental factors including individual habits such as smoking, nutrition, and so on should also seriously be considered. It is conceivable that the dose response at the low dose range could be interpreted from that of high dose range rather than direct observation of dose response at low dose range as described heretofore. Analysis of the shape of dose response at all dose ranges was made in the aforementioned data set i.e. cancer mortality and incidence, using the basic model for dose response, including linear, linear quadratic and pure quadratic with or without cell-killing. In general, the analysis failed to distinguish statistically any particular model in dose response with the actual data sets using the fitness of model.

A-bomb survivors data being considered to be most reliable source of information for radiation effects on human beings, the results have been widely referred to in the literature including UNSCEAR, ICRP and BEIR report. Yet, it is difficult to determine the shape of the dose-response at the low dose range.

Many epidemiological studies on radiation effects on man have been referred to Dr. Lucky including medical x-ray, natural background radiation, and occupation exposure to radiation. It is obvious that great caution should be exercised in the interpretation of these epidemiological data.

Summary

An analysis of the dose response within the low dose range (defined here

as doses of less than 50 rad) was conducted among A-bomb survivors in the ABCC-RERF cohort in an attempt to detect the phenomenon of radiation hormesis, if indeed present. These studies included as endpoints cancer mortality, cancer incidence, frequency of cells with chromosomal aberrations, PHA response of peripheral lymphocytes and frequency of mental retardation among survivors exposed in utero. In general, the dose response of these indices of radiation damage varied among comparison groups within the low dose range but failed to suggest the existence of radiation hormesis.

A great caution is necessary in the interpretation of dose-response derived from epidemiological data on radiation effects in man, including studies on effects of exposure to medical x-ray, occupational exposure and natural background radiation.

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