CANCER RISK AMONG ATOMIC BOMB SURVIVORS

Kiyohiko Mabuchi,[1] D.A. Pierce,[1] D.L. Preston,[1] Y. Shimizu,[1] and M. Vaeth[2]

[1]Radiation Effects Research Foundation Hiroshima, Japan
[2]University of Arhus, Arhus, Denmark

The Radiation Effects Research Foundation (RERF) and its predecessor, the Atomic Bomb Casualty Commission (ABCC), has been conducting a long-term follow-up of a cohort of the atomic bomb survivors in Hiroshima and Nagasaki. The continuing follow-up of this population, known as the Life Span Study (LSS) cohort, has been a major source of epidemiological data for radiation risk assessment (1, 2). Periodic analyses of the LSS mortality data have resulted in a series of reports that describe and quantify radiation effects on cancer mortality (3). More recently, a series of comprehensive reports of cancer incidence for this cohort has also been published (4-7). The latest report on the LSS cancer mortality data through 1990 will soon be published. The purpose of this presentation is to provide an updated overview of the LSS cancer and leukemia data.

LIFE SPAN STUDY

Population

The LSS cohort includes most survivors within 2.5 km of the bombings who lived in Hiroshima or Nagasaki in 1950 and who met certain conditions that were considered favorable for follow-up. The cohort also includes a sample of survivors who were within 2.5 - 10 km of the hypocenter; this group was chosen to be of the same size and to have the same age and sex distribution as the original group of more proximally exposed survivors. The portion of the LSS cohort used in the latest analysis includes about 86,500 survivors for whom DS86 radiation dose estimates are currently available (8, 9). This represents 93% of all the survivors in the cohort, and consists of 34,300 survivors with estimated doses less than 0.005 Gy kerma and 52,200 with estimated doses of 0.005 Gy or higher (a mean dose of 0.26 Gy). The LSS data are characterized primarily by acute exposure to low LET gamma radiation, with a non-negligible neutron component in Hiroshima. However, the 37,000 subjects in the dose range of .005 - .20 Gy can also provide useful information on low-dose effects.

Follow-up

Mortality follow-up for the period from 1950 onward has been undertaken using regular checks on the vital status of all cohort members based on the Japanese family registration system known; causes of death are obtained from information recorded on death certificates. This method of follow-up provides virtually complete ascertainment of vital status and mortality data. The LSS cancer incidence data that have recently become available from the Hiroshima and Nagasaki tumor registries provide better diagnostic information and improve ascertainment of relatively non-fatal cancers; these are an important complement to the mortality data. A subset of the LSS cohort has been followed by biennial health examinations under the Adult Health Study program, providing longitudinal data on disease morbidity and health status. These mortality and morbidity follow-up data enable comprehensive analyses of a wide spectrum of health outcome associated with radiation exposure from the atomic bombings.

RESULTS TO DATE

At the end of 1990, 56% of the LSS cohort members were alive while most of those exposed at middle ages or later in life had died (Table 1). However, it is particularly important to note that some 85% of those exposed at ages less than 30 years are still alive

Table 1
Cohort survival by age at exposure

Age at exposure	People in 1950	Percent alive in 1990
0-9	17,824	94
10-19	17,557	86
20-29	10,882	77
30-39	12,270	51
40-49	13,489	16
50 +	14,550	1
Total	86,572	56

Excess cancer deaths

Excess leukemia deaths among the atomic bomb survivors became apparent a few years after the bombings, reaching a peak 5-10 years after the exposure, followed by a gradual decline. Since 1950, a total of 249 leukemia deaths occurred in 86,500 survivors in the LSS cohort. Of these, 86 leukemia deaths are considered as excess deaths due to radiation, and these account for 49 % of 176 leukemia deaths in the 52,200 subjects with significant exposures (Table 2).

Table 2
Cancer deaths among 52,200 A-bomb survivors with significant exposures
1950-1990

	Total number of deaths	Estimated number of deaths due to radiation exposure	% attributable to radiation exposure
Leukemia	176	86	49%
Other types of cancer	4,687	341	7%
Total	4,863	427	9%

Excess deaths from cancers other than leukemia emerged 5-10 years after the exposure. To date, a total of 4,687 deaths from cancers other than leukemia have occurred in 52,200 survivors with significant exposures in the LSS cohort (Table 2). Of these, 341 or 7 %, are considered to be associated with radiation exposure. Thus, for cancers other than leukemia, or solid cancers, the proportion of deaths due to radiation is much smaller than for leukemia but the absolute number of excess deaths is much larger.

Temporal patterns of cancer risk

The long-term follow-up of the LSS provides a unique opportunity to examine the temporal patterns of cancer and leukemia risk as they are affected by age at exposure and sex. As evident from the discussion below, understanding of such temporal patterns is essential in risk assessment. The age-dependent temporal patterns are strikingly different for solid cancers and leukemia. Figure 1 depicts the age and sex dependent temporal patterns of solid cancer risk. One of the most important findings here is that, for those exposed as adults, the excess relative risk per unit radiation dose (ERR) of solid cancers has been remarkably constant over the follow-up period. This means that the excess absolute risk has increased over the entire follow-up period roughly in proportion to the rapid age-specific increase of the background risk. For those exposed as children, the ERR of solid cancers, which was especially high in the early years of follow-up, has been found to be decreasing over time. Since the very high ERR for this group early in the follow-up is based on a very small background risk at young ages, the absolute risks for the young survivors are still relatively small. Because of the large number of the young subjects who are yet to be followed, how the solid cancer risk will behave for the young survivors in the future is one of the main remaining questions.

The ERR for solid cancer is also higher for women than men. However, in interpreting the sex difference in ERR, one must keep in mind that the background rates for men are at least twice as high as for women. The absolute risk for cancers other than leukemia is quite similar for men and women.

In sharp contrast to the solid cancer deaths, most of the excess leukemia deaths occurred early in the follow-up. Patterns of risk for leukemia are shown in Figure 2. Generally the excess relative risk decreases with time (or with aging), but the rate of decrease in the risk is lower (or the decrease is less rapid) for those exposed at older ages. Particularly among those exposed as children, essentially all of the excess deaths occurred during the several years after the exposures. On the other hand, among those exposed as adults, the excess risk persists at low levels throughout the entire follow-up period.

Dose response curves

Another important finding from the LSS follow-up data is a striking difference in the shape of a dose response curve for solid cancers and leukemia. The dose response curve for solid cancers is unequivocally linear whereas there is a statistically significant upward curvature in the leukemia dose response curve up to about 3 Gy. The difference in dose response curve for solid cancers and leukemia may reflect different underlying mechanisms for carcinogenesis and leukemogenesis, as the former is known to involve multi-step processes and multiple factors whereas for the latter chromosomal rearrangements are of primary importance.

The low dose extrapolation factor (LDEF) is the adjustment factor to be applied to linear risk estimates in extrapolating the excess risk to low doses. The shape of the dose response curve for solid cancers and leukemia has been analyzed using the LSS data (10,11). Based on the LSS incidence data, LDEF values for solid cancers were in a narrow interval around 1, with a value of 1.4 or greater being inconsistent with the data. For leukemia, the best fitting LDEF value was 2.5 with but a value as high as 10-15 could not be ruled out.

Lifetime risk projection

The LSS cancer data are used by various national and international organizations concerned with radiological protection. In setting up safety standards, considerations are given to projected life time risk estimates and other measures of health detriment attributable to radiation exposure. At the present time, one of the most important sources of uncertainty in lifetime risk estimates is the projection that must be made from the incomplete follow-up. This is especially true for those exposed at young ages.

To examine the effect of different assumptions about the future course of the solid cancer risk, the UNSCEAR 1994 Report used three different models in projecting the lifetime risk that an individual would die from cancer (or leukemia) as a result of exposure to radiation (Table 3). In one model, the ERR for solid cancer is assumed constant throughout the lifetime of the survivors. This is a commonly used method but seems somewhat unreasonable since it is now clear that the solid cancer ERR among young survivors has been decreasing over the follow-up. In two alternative models, the solid cancer ERR for the survivors who were less than 45 years old at exposure is assumed to decrease linearly starting 45 years after exposure but at different rates of decrease. The excess leukemia risk in the LSS occurred mostly in the early years of follow-up and appears to be decreasing for the youngest survivors. Therefore, there is no need to consider different projection models.

Table 3

Comparison of estimates of lifetime risk of mortality form solid cancers and leukemia following acute whole-body exposure to 1 Sv

(from UNSCEAR 1994 Report)

Projection method	**Lifetime risk in percent**	**Years lost per case**
Solid cancers		
Constant relative risk [a]	10.9	11.6
Decline to risk for age at exposure 50 [b]	9.2	12.3
Declines to zero risk at age 90 years [c]	7.5	13.3
Constant relative risk (UNSCEAR 1988)	9.7	11.4
Leukemia		
Linear-quadratic dose response model	1.1	31
Constant relative risk (UNSCEAR 1988)	1.0	26

[a] ERR constant from 10 years after exposure

[b] ERR constant for first 45 years after exposure; risk then decreases linearly with age. At attained age 90 years, the risk is equal to that for a person aged 50 years at exposure

[c] ERR constant for first 45 years after exposure; risk then decreases linearly with age. At attained age 90, the risk is equal to that for a person aged 50 years at exposure.

COMMENT

The LSS cohort data have provided unique opportunities for elucidating the nature and magnitude of risk associated with radiation exposure as it is affected by sex, age and time. With only about 50% of the subjects for whom the follow-up has been completed, there clearly is still much to be learned from the future follow-up. The most important uncertainty at the present time relates to the temporal pattern of solid cancer risk of those survivors who were exposed early in life. How the risk for this group of young survivors will behave in the future is one of the most important remaining questions. Although the patterns of leukemia risk are much more complex than those for solid cancers, most of the excess deaths occurred in the early years of follow-up. There appears much less uncertainty with respect to risk estimates for leukemia, although continued work is also important to obtain a complete picture on the temporal distribution of leukemia risk.

Figure with legend

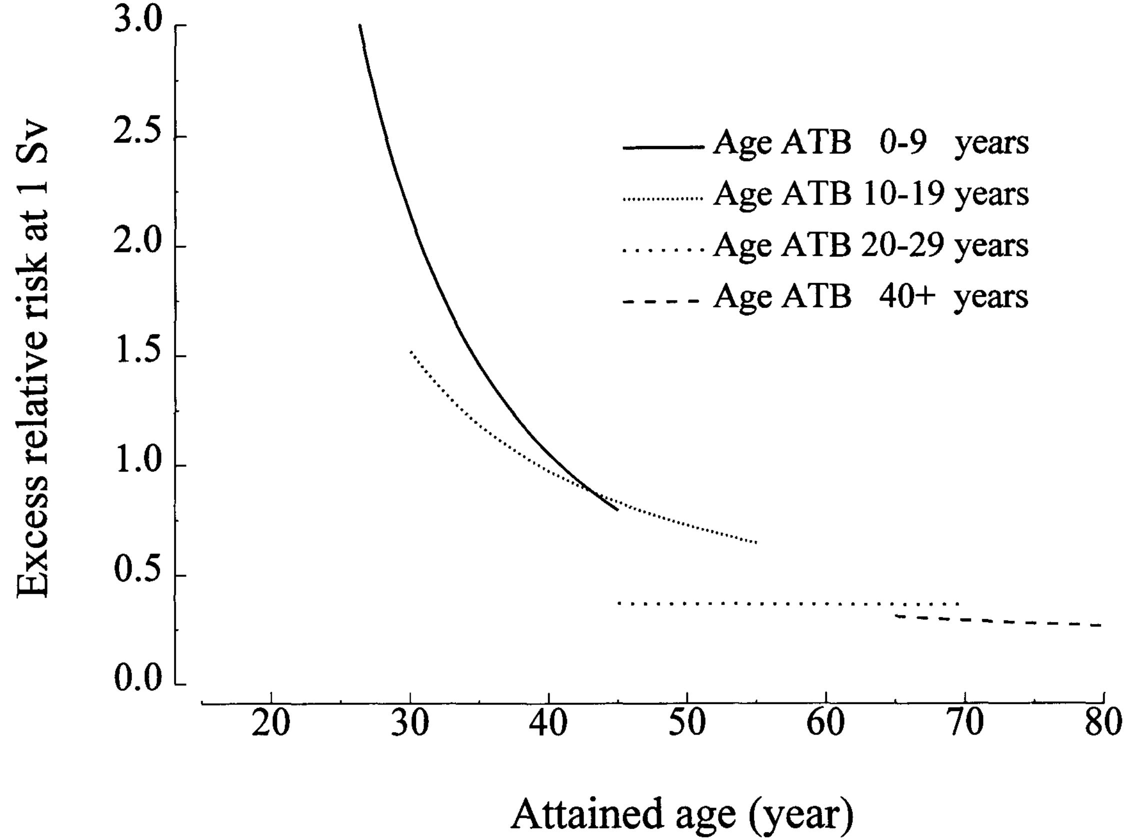

Figure 1. Temporal patterns of solid cancer risk

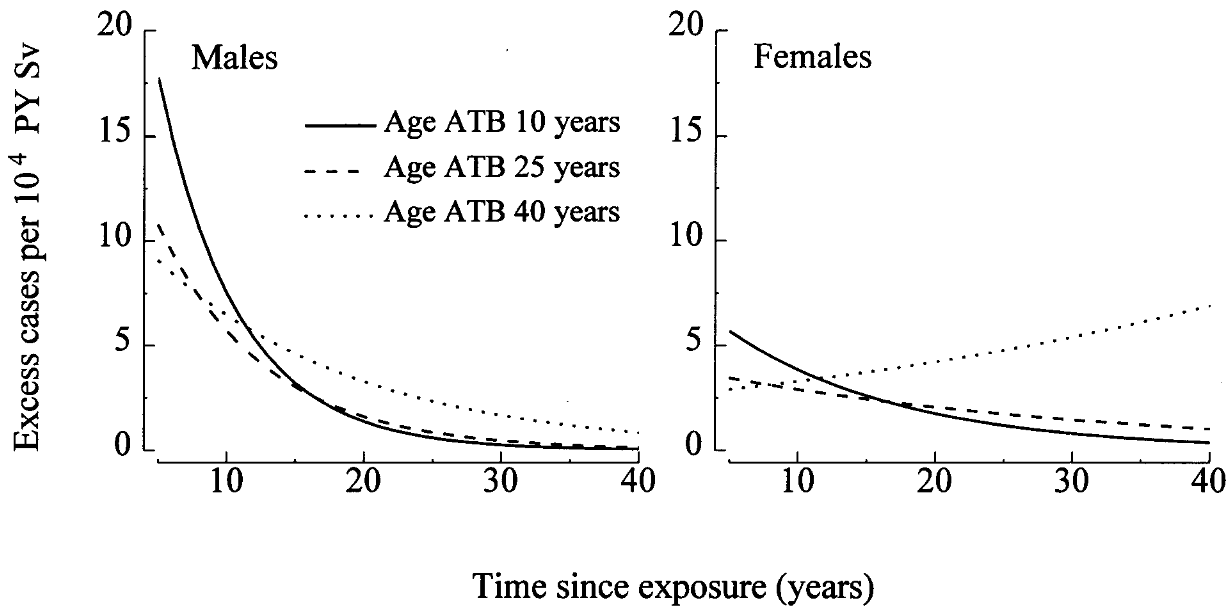

Figure 2. Temporal patterns of leukemia risk

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