Risk of Cancer among Atomic Bomb Survivors

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(Received December 6, 1990)

Atomic bomb survivors/Cancer risk/Dosimetry/Dose-response/Latency

This report describes the risk of cancer and in particular cancers other than leukemia among the survivors of the atomic bombing of Hiroshima and Nagasaki. Attention focuses primarily on the risk of death from cancer among individuals in the Life Span Study sample of the Radiation Effect Research Foundation in the period 1950–1985 based on the recently revised dosimetry, termed the DS86 doses.

Mortality from malignant tumors is increased among A-bomb survivors as a late effect of A-bomb radiation. Besides the well-known increase of leukemia, there also has been demonstrated increase of cancer of the lung, breast, esophagus, stomach, colon, ovary, urinary bladder, thyroid, and of multiple myeloma, but no increase has yet been observed in mortality from cancer of the rectum, gallbladder, pancreas, prostate and uterus, and of malignant lymphoma.

The pattern of appearance over time of radiation-induced cancer other than leukemia differs from that of leukemia. In general, radiation-induced solid cancer begins to appear after attaining the age at which the cancer is normally prone to develop (so-called cancer age), and continues to increase proportionately with the increase in mortality of the control group as it ages.

Sensitivity to radiation, in terms of cancer induction, is higher for persons who were young at the time of the bomb (ATB) in general than for those who were older ATB. Furthermore, susceptibility to radiation-induced cancer tends to be higher in pre- than in post-natally exposed survivors (at least those exposed as adults).

Other radiation effect modifiers and the shape of the dose response curve will also be discussed.

INTRODUCTION

Atomic bombs were dropped on Hiroshima and Nagasaki in August 1945. Although the number of deaths immediately attributable to the bombings is not known precisely, it has been estimated that somewhere between 90,000 and 120,000 individuals out of a population of approximately 330,000 in Hiroshima died due to their exposure to ionizing radiation, from burns or mechanical injuries, or some combination of these causes. The corresponding figures in Nagasaki are 60,000 to 80,000 out of around 250,000 persons.

The first nationwide survey of atomic bomb survivors was conducted in October 1950, five years after the bombing. Throughout the country, 284,000 survivors were enumerated. As a study group, about 120,000 exposed and non-exposed individuals were selected from among the survivors resident in Hiroshima and Nagasaki at the time of this census, or through special surveys conducted in these cities shortly after the national census. This
group, or cohort, is called the Life Span Study Sample. Mortality among these individuals has been under study since 1950. Deaths are routinely identified through the obligatory household registries that exist in Japan, and ascertainment is essentially complete. Periodic analyses of the deaths occurring in the Life Span Study Sample continue, and undoubtedly will for some time to come.

The most recent results of the Life Span Study cover the period 1950–85, and it is these results that are briefly presented here.\textsuperscript{1,2} They are based on the revised dose system, referred to as the Dosimetry System 1986 (DS86).

**DOSIMETRY**

Radiation related risks among the A-bomb survivors have heretofore generally been analyzed in terms of a system of dosimetry introduced in 1968, known as the T65DR doses.\textsuperscript{3} Recently, however, a new dosimetry system was developed for the estimation of individual doses, termed the Dosimetry System 1986 (DS86).\textsuperscript{4} This system takes into account a survivor's distance from the epicenter, shielding, posture, orientation, and age. In 1988, when the analysis described here was begun, DS86 doses were available on 83% of the 91,000 members in the sample who have T65DR doses; however, within the past two years, doses have been estimated on an additional 12,000 or so persons so that now doses are available on about 95% of the sample.

The DS86 free-in-air gamma dose increases somewhat in Hiroshima, but decreases in Nagasaki in comparison with the T65DR estimates; whereas the neutron dose decreases to about 10% its former value in Hiroshima and 30% in Nagasaki.\textsuperscript{1,4,5} For kerma in Japanese houses, the average transmission factor for gamma rays, but not neutrons changes substantially, form 0.90 in the T65DR to 0.46 in the DS86. Accordingly, the DS86 estimates of shielded kerma are lower than the T65DR estimates. For organ doses, the transmission factors are higher than in the T65DR system. Since the changes in the transmission factors for house shielding and organ tissue are in the opposite direction, they tend to nullify one another, and as a result, organ doses do not change much from the T65DR dosimetry to the DS86.

Assuming a linear model, an RBE of 1, and using organ-absorbed dose, the risk coefficients derived from the two dosimetry are very similar; whereas those based on shielded kerma are about 40% higher with the new doses.\textsuperscript{1,5} If RBE values larger than 1 are assumed, the disparity between the two dosimetry increases because the neutron dose is much greater in the T65DR. At an RBE of 10, for the five specific cancers, i.e., female breast, colon, leukemia, lung, and stomach, the increase in excess number of deaths per 10\textsuperscript{4} PYSv under the DS86 varies from 12% (colon) to 133% (female breast). The change in dosimetry does not alter the list of radiation-related cancers; that is to say, there are no cancers previously believed to be radiation-related that are now no longer so. Some city differences in dose-response thought to be real in the past, when the T65DR doses were used, are not significant with the DS86 doses.\textsuperscript{1,5}
Mortality from leukemia has long been known to be increased among A-bomb survivors, and mortality from malignant tumors other than leukemia has also increased. However, an increased risk has not been observed for all cancer sites. Figure 1 shows the relative risk (at 1 Gy) of cancer mortality by site with the 90% confidence limits for the period 1950–85. It will be noted that, in addition to leukemia, cancers of the esophagus, colon, stomach, lung, breast, ovary, urinary tract, and multiple myeloma are also increased significantly. However, there has been no demonstrable increase as yet in mortality from cancers of the rectum, pancreas, uterus, prostate, or malignant lymphoma. Thus, sensitivity to the induction of cancer following exposure to ionizing radiation seems to differ by site. This conclusion must be guarded, however, since, with the exception of leukemia, the excess risk manifests itself only after the exposed individuals reach the age at which cancer is normally prone to develop. The latter age differs from organ to organ, and an increase in risk for those cancers in which no increase has yet been observed may occur in the future.

**EFFECT OF AGE AT TIME OF BOMBING (ATB) ON CANCER MORTALITY**

Radiation effects are significantly modified by an individual’s age at the time of bombing (ATB). Figure 2 shows the relative risk of deaths at 1 Gy for all cancers except leukemia and for specific cancer sites. The relative risk tends to be higher for survivors who were young at the time of bombing. Since ages attained are different among age ATB cohorts,
the effects of age ATB should be examined by the attained age. The relative risk tends to be higher in those of younger age ATB among those of the same attained age. This emphasizes that sensitivity to radiation carcinogenesis differs by age ATB and that the sensitivity is higher the younger the age ATB.

In this connection, we describe briefly recent studies of cancer incidence among the prenatally exposed survivors. This study has examined the risk of cancer incidence over a period of 40 years, that is 1945–84, among a total of 1,829 in utero exposed survivors. This study adds eight years of follow-up to a previous report which was confined to mortality. Only two cases of childhood cancer were observed among these survivors in the first 14 years of life; both had been heavily exposed. Subsequent cancers have all been of the adult type. The risk of all cancers has been compared with A-bomb survivors aged 0–9 ATB (Table 1). It should be noted that the estimate of the cancer risk among A-bomb survivors 0–9 ATB is based on cancer mortality, while the estimate among the in utero exposed is based on cancer incidence. However, nearly identical average excess risks are seen. The relative risk of cancer is higher the younger the age ATB as mentioned before. Comparison of in utero exposed survivors with exposed adults shows the cancer risk to be higher in the former than
in the latter. This raises the possibility that radiation-related cancers will increase as the prenatally exposed survivors become older.

Survivors who were exposed at younger age including in utero exposure have just reached the age at which cancer is normally prone to develop and they have an especially high risk in association with radiation dose. Therefore, it is important to continue careful long term follow-up of these cohorts.

### TEMPORAL PATTERN OF RADIATION INDUCED CANCER

Radiation effects do not appear immediately after exposure but occur some years later. For leukemia, the latent period is short. Radiation-induced leukemia occurred 2–3 years after exposure and reach its peak within 6–8 years after the bombing and has since declined steadily. However, this has not been true for solid tumors, such as lung cancer.

Figure 3 shows the cumulative mortality rate for this malignancy by radiation dose and age at the time of the bombing. For age 30–39 years and over ATB cohorts, an excess in the cumulative death rate from lung cancer appears around 1965 and continues to increase with time. For younger age ATB groups, the excess appears later. Thus, it could be said that radiation induced solid cancers, such as lung, begin to appear after the survivors reach those ages at which cancer is normally prone to develop. This suggests that for solid tumors radiation only induces the first mutational step in the transformation of a normal cell to a malignant one, and that a second, and possibly other promotional steps, must occur before a tumor actually develops.

Figure 4 shows the change in relative risk at 1 Gy in leukemia and all cancers except leukemia mortality for successive five-year periods of surveillance after 1950. The RR of

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**Table 1. Comparison of Cancer Risk Between “In Utero Exposed” and “Exposed at 0–9 Age at the Time of Bombing (ATB)”**

<table>
<thead>
<tr>
<th></th>
<th>In Utero (1950–84)</th>
<th>0–9 Age ATB (1950–85)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DS86 Uterus Dose</td>
<td>DS86 Tissue Kerma</td>
</tr>
<tr>
<td>No. of cancer</td>
<td>18 (2)*</td>
<td>142 (31)*</td>
</tr>
<tr>
<td>RR at 1 Gy</td>
<td>All cancer 3.77 (1.1, 13.5)</td>
<td>All cancer 3.97 (2.9, 5.4)</td>
</tr>
<tr>
<td></td>
<td>Leukemia 17.25 (9.3, 38.9)</td>
<td>Other cancer 2.23 (1.6, 3.4)</td>
</tr>
<tr>
<td>Excess Risk /10⁸ Person</td>
<td>All cancer 6.57 (0.47, 14.5)</td>
<td>All cancer 5.47 (3.54, 7.17)</td>
</tr>
<tr>
<td></td>
<td>Leukemia 2.93 (2.23, 3.60)</td>
<td>Other cancer 2.27 (1.11, 3.65)</td>
</tr>
</tbody>
</table>

( ): 90% confidence interval
( )*: No. of cases of leukemia
Source: Perinatal and Multigeneration Carcinogenesis
Ed. N.P. Napalkov, J.M. Rice, L. Tomatis & H. Yamasaki
leukemia has decreased since 1950. However, the RR is still significantly elevated in the years 1950–85, but only in Hiroshima. When examined by age at the time of bombing (ATB), the continued excess of leukemia is limited to those survivors who were 30–49 years of age ATB. For those survivors under the age of 30 ATB, no excess deaths have been observed after 1970. Similarly no excess is observed among those survivors 50 years of age or older ATB in the period 1980–85, probably because the number of such survivors alive in 1980 was small. The temporal distribution of risk of leukemia is different by age ATB, and type of leukemia. It has been shown that the younger the age ATB, the greater
was the risk of leukemia in the early years following the bombing, and the more rapid was the decline in risk thereafter. Acute forms of leukemia are primarily responsible for these trends. 6)

For solid tumors, the excess risk became significant about 1960, roughly fifteen years after exposure, and continues over time.

In estimating lifetime risk of radiation-induced cancers for all sites except leukemia, two risk projection models have been conventionally used, namely, (a) the multiplicative or constant relative risk model, which assumes the risk to be a constant proportion of the "natural" or background rate, and (b) the additive or constant absolute risk model, which assumes the risk to be a constant independent of the "natural" rate. To determine which model fits the observed data better, the relative risk (at 1 Gy) and excess deaths per 10^4 person years per Gy for all cancers except leukemia were examined by age at death for specific age ATB cohorts (Table 2).

As will be noted, the relative risk is almost constant for the specific age ATB cohorts, except for the cohort under the age of 10 ATB. This tendency is clearer when the minimum latent period, assumed to be 10 years, is taken into account and the values in parentheses in the table are excluded. For the youngest cohort, unlike the older ones, the time from exposure to death (a measure of the latent period) is shortened in the high dose group, and the RR decreases with time under 30 years of attained age and then levels off. The absolute risk (excess deaths per 10^4 person-years per gray), as shown in this table, rises with attained age in all age ATB cohorts. Thus, the present analysis still favors the constant relative risk (or some modification of it) over the constant absolute risk model.
With respect to specific sites of cancer, the tendency is similar, although the variation is greater than that seen for all cancers except leukemia. None of the specific sites exhibits a statistically significant change, although at face value lung cancer seems to show a decreasing tendency.

The temporal distribution of risk among the A-bomb survivors appears to be different from that in the ankylosing spondylitis patients who show a decline in cancer risk after 25 years following irradiation.8

### Table 2. Relative Risk at 1 Gy and Excess Death (per 10^4 PYGy) for All Cancers Except Leukemia by Age at the Time of Bombing (ATB) and Age at Death (ATD), (Shielded Kerma)

<table>
<thead>
<tr>
<th>Age ATB</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70+</th>
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<tbody>
<tr>
<td>Relative risk at 1 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;10</td>
<td>(70.07)</td>
<td>5.89</td>
<td>1.96</td>
<td>1.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>(40.90)</td>
<td>(0.82)</td>
<td>1.66</td>
<td>1.59</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>(1.38)</td>
<td>2.09</td>
<td>1.74</td>
<td>1.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>(0.84)</td>
<td>(1.12)</td>
<td>1.11</td>
<td>1.23</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>(1.25)</td>
<td>(1.12)</td>
<td>1.13</td>
<td>1.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>(2.58)</td>
<td>(0.95)</td>
<td>1.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>75.32</td>
<td>2.22</td>
<td>1.60</td>
<td>1.58</td>
<td>1.39</td>
<td>1.13</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Excess death (per 10^4 PYGy)</th>
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<tbody>
<tr>
<td>&lt;10</td>
</tr>
<tr>
<td>10–19</td>
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<tr>
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<td>30–39</td>
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<tr>
<td>40–49</td>
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<tr>
<td>50+</td>
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<tr>
<td>Total</td>
</tr>
</tbody>
</table>

( ): Before the assumed minimum latent period of 10 years.
Source: Radiation Research 121:120–141 (1990)

With respect to specific sites of cancer, the tendency is similar, although the variation is greater than that seen for all cancers except leukemia. None of the specific sites exhibits a statistically significant change, although at face value lung cancer seems to show a decreasing tendency.

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### SHAPE OF THE DOSE-RESPONSE CURVE

Figure 5 shows the observed and fitted dose-response curves for leukemia and all cancers except leukemia. In both instances, at 2 Gy and over, a downward curvature is observed. Under 2 Gy, the curvature is upwards for leukemia, but not for all cancers except leukemia where the response is linear.

To determine the shape of the dose-response curve a variety of models were fitted. For leukemia, when the entire dose range is considered, a linear-quadratic (LQ) model with
provision for a downwards curvature at the high doses (the LQ-K model) fits better than the linear (L) model, but the LQ model does not fit better than the L model. However, when the dose range is restricted to doses under 2 Gy, the LQ model fits better than the L model. For all cancers except leukemia, non-linear models do not fit any better than the linear model, regardless of whether the dose range is restricted or not.

Table 3 was constructed to determine the lowest dose interval where a statistically
significantly higher cancer mortality occurs than that seen in the control (0 Gy) group. The lowest dose interval at which a significant increase in the frequency of leukemia or all other cancers can be demonstrated is 0.20–0.49 Gy. Thus, the experience of the survivors continues to provide little direct insight into the shape of the dose response curve at low doses. However, it should be noted, that when the survivors are divided into two groups, those receiving a dose of less than a half gray and those receiving more, the excess relative risk of leukemia is 2.44 in the former group and 5.53 in the latter (this difference is statistically significant), and this suggests a linear-quadratic response. A similar difference is not seen for all cancers other than leukemia where the comparable excess relative risks are 0.37 and 0.42, respectively. The data are still too sparse to examine the solid tumors on a site-specific basis with much reliability.

REFERENCES