Dose-response Relationship for Lifetime Excess Mortality and Temporal Pattern of Manifestation in Mice Irradiated Neonatally with Gamma Rays

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Lifetime risk / Excess mortality / Dose-response / Neonatal mice / Gamma rays

The dose-response relationships for the lifetime excess mortality and temporal distribution of excess mortality were analysed using a data set from an experiment on the long-term effects of gamma irradiation in neonatal mice. The excess mortality was calculated based on an assumption that any increase in the mortality rate was attributable to radiation exposure. The dose-response relationship for the lifetime excess mortality was convex upward, whereas the shortening of the mean life span was proportional to the dose. The excess mortality at 1 Gy was estimated to be 35.6%. The relative risk decreased markedly with increasing age. However, the mortality rate in the irradiated group was persistently higher than the background rate of death, and the absolute risk increased with age. A logistic specification was used to analyze the temporal distribution of the excess mortality. The results of the analysis indicated a dose-dependent shortening of the latent period and a broadening of the distribution.

INTRODUCTION

The present study was aimed to elucidate the shape of the dose-response relationship for the lifetime excess mortality and the temporal pattern of manifestation in mice irradiated neonatally with gamma rays. The lifetime excess mortality was calculated from the increase in the mortality rate after irradiation, which is one of the characteristic features of the long-term effects of ionizing radiation. In earlier studies on the long-term effects of radiation it was argued whether this increase in the mortality rate is due to a non-specific acceleration of aging, or to the induction of specific lethal diseases. The United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) reviewed the results of epidemiological and experimental studies on the long-term effects of radiation in a 1982 report and concluded that the increase in the mortality rate by radiation is largely attributable to the induction of cancer. The majority of subsequent studies have confirmed this conclusion. The life span study of atomic-bomb survivors, however, has shown an increase in the mortality rate from causes of death other than cancer, although a non-specific acceleration of aging was not detectable. Also, experimental studies have shown that ionizing radiation induces lethal non-cancer diseases. Although the lifetime risk of radiation for cancer has been estimated with projection models, a large number of uncertainties remain. The lifetime risk for the induction of non-cancer disease has not been estimated by the international organization for radiation protection.

Information from life span studies of laboratory animals may be useful as a basis for estimating the lifetime risk of ionizing radiation. Prentice et al.
examined the effects of gamma rays on the mortality rate in mice using data from Oak Ridge National Laboratory\textsuperscript{20}. Dose-response relationships for the mortality rate from all causes of death and from specific neoplastic disease and the temporal pattern of manifestation were analyzed using the proportional hazard method. The overall mortality rate clearly increased in the irradiated population, and the relative risk was found to decrease with the time since exposure. This study indicated that the increase in the overall mortality rate after irradiation is valuable as a comprehensive measure of the long-term effects of radiation. Storer et al. examined the relationship between the susceptibility to radiogenic carcinogenesis and the spontaneous incidence of neoplastic disease\textsuperscript{21}. They showed that the relative risk estimates were almost identical beyond the differences of the animal strain and species for several types of neoplasms. This finding is biologically interesting and important as a basic principle of risk estimation. Carne et al. compared the life-shortening effects in mice and dogs irradiated continuously with \textsuperscript{60}Co gamma rays\textsuperscript{22}. The relative risk for the mortality rate was found to be almost identical in both species when animals were irradiated at the same dose rate. These studies showed that experimental investigations using laboratory animals can provide valuable information concerning risk assessment.

In a previous report, we described a method for estimating the lifetime risk from all causes of death after exposure to radiation\textsuperscript{23}. This lifetime risk from all causes of death was estimated from the increase in the mortality rate based on the assumption that the increase in the mortality rate is attributable to exposure to radiation. The age-dependence of the susceptibility and the dose-response relationship were analyzed using the lifetime risk from all causes of death as a comprehensive measure of the long-term effects of radiation. Mice from the neonatal to puberty period were found to be highly susceptible to radiation-induced lifetime risk. The dose-response relationship for lifetime risk was analyzed for mice irradiated neonatally with gamma rays. The shape of the dose-response curve was concave upward for the lifetime relative risk, and was convex upward for the lifetime excess mortality. However, the sample size was not sufficient for a detailed analysis. Therefore, we conducted a larger scale experiment in which mice were irradiated neonatally with graded doses of gamma rays ranging from 48 to 285 cGy. Using these experimental data, the dose-response relationships for solid tumors were examined in a previous study\textsuperscript{24}. In this work, a further analysis was made on the lifetime risk from all causes of death and on the temporal pattern of manifestation.

**MATERIALS AND METHODS**

**Data set for analysis**

Data from a life span experiment were used for the present study. Female B6C3F\textsubscript{1} mice were irradiated with 48, 95, 143, 190, 238 or 285 cGy gamma rays from \textsuperscript{137}Cs at a dose rate of 87 cGy per minute within 24 hours after birth. All of the mice were allowed to live out their entire life span under a specific pathogen-free condition. The sample size of each group is listed in Table 1. The detailed conditions of the experiment were described in a previous report in which the dose-response relationship for the induction of solid tumors was analyzed\textsuperscript{24}.

**Methods of analysis**

The mortality rate at a specific interval of age (\(\lambda_i\)) was represented as the number of deaths (\(n_i\)) per mouse day at risk (\(m_i\)): \(\lambda_i = n_i/m_i\). The standard error of the mortality rate was obtained based on the assumption that the number of deaths during a specific age interval had a binominal distribution. The relative risk (\(rr_i\)) was defined as the ratio of the mortality rate in the group irradiated with dose \(D\) to that in the control group: \(rr_i = \lambda_i(D)/\lambda_i(0)\). The absolute risk was defined as the difference between the mortality rate in the irradiated group and that in the control group: \(ar_i = \lambda_i(D) - \lambda_i(0)\).

Animals exposed to radiation die from radiation-induced and spontaneous causes. Therefore, the excess number of deaths (\(N_{exc}(D, T)\)) until age \(T\) in group...
Table 1. Sample size, mean life span, lifetime relative risk, lifetime excess mortality and temporal variation of the cumulative mortality.

| Dose (cGy) | 0     | 48    | 95    | 143   | 190   | 238   | 285   |
|------------|-------|-------|-------|-------|-------|-------|-------|
| Number of mice | 885   | 453   | 338   | 331   | 332   | 206   | 272   |
| Mean life span, days±SE* | 864.8±4.6 | 842.0±6.4 | 807.9±7.4 | 785.6±7.8 | 758.1±7.5 | 721.2±10.7 | 700.1±9.9 |
| Lifetime relative risk, ±SE* | 1.205±0.058 | 1.542±0.084 | 1.812±0.100 | 2.313±0.133 | 2.892±0.196 | 3.487±0.222 |
| Lifetime excess mortality, ±SE* | 0.170±0.045 | 0.352±0.049 | 0.448±0.048 | 0.568±0.048 | 0.654±0.058 | 0.713±0.050 |

Cumulative mortality until age (days):

| 250 | 0.001±0.001 | 0.004±0.002 | 0.008±0.006 | 0.003±0.002 | 0.003±0.002 | 0.015±0.002 | 0.026±0.002 |
| 450 | 0.007±0.003 | 0.008±0.003 | 0.027±0.009 | 0.033±0.009 | 0.033±0.009 | 0.049±0.013 | 0.088±0.014 |
| 550 | 0.019±0.005 | 0.027±0.007 | 0.052±0.012 | 0.048±0.012 | 0.078±0.015 | 0.131±0.023 | 0.154±0.021 |
| 650 | 0.063±0.008 | 0.068±0.017 | 0.109±0.018 | 0.154±0.025 | 0.192±0.023 | 0.281±0.034 | 0.272±0.029 |
| 750 | 0.179±0.014 | 0.236±0.021 | 0.286±0.027 | 0.356±0.030 | 0.418±0.032 | 0.514±0.044 | 0.574±0.039 |
| 850 | 0.450±0.020 | 0.482±0.029 | 0.623±0.037 | 0.643±0.038 | 0.748±0.040 | 0.805±0.052 | 0.853±0.046 |
| 950 | 0.727±0.042 | 0.793±0.035 | 0.802±0.042 | 0.905±0.043 | 0.937±0.044 | 0.966±0.056 | 0.993±0.048 |
| 1050| 0.910±0.026 | 0.954±0.037 | 0.976±0.044 | 0.987±0.045 | 0.991±0.045 | 1.000±0.057 | 1.000±0.048 |
| 1150| 0.987±0.027 | 0.991±0.038 | 1.000±0.045 | 1.000±0.045 | 1.000±0.045 | 1.000±0.045 |
| 1250| 0.992±0.026 | 1.000±0.039 |         |         |         |         |         |

*SE: standard error
method and the weighting factor was the reciprocal of the obtained value. Temporal variations of mortality rate, absolute risk, relative risk, cumulative relative risk and cumulative excess mortality were described in detail. The logistic function was fitted to the temporal variation of the cumulative excess mortality, and the parameters of the logistic function were also obtained by a regression analysis.

RESULTS

Dose-response relationship for lifetime risk

The mean life span, lifetime relative risk and lifetime excess mortality are summarized in Table 1 together with standard errors. These are comprehensive measures of the long-term effects of ionizing radiation. Life-shortening (LS(D)) was proportional to dose in the dose range examined here,

\[ \text{LS(D)} = aD. \quad (3) \]

The value of parameter \( a \) was estimated to be 0.000670, and its standard error was 0.000011. Because the linear model fitted well the dose-response relationship for the life-shortening effect, the results of fitting other models are not shown.

The lifetime relative risk for the mortality rate increased with increasing the dose of gamma rays. As shown in the left panel of Fig. 1, the dose-response curve for the lifetime relative risk was concave upward. The fitting of the mathematical models to the dose-response relationship for the lifetime relative risk was examined by a regression analysis. The values of Akaike’s information criterion (AIC) for the exponential, linear-quadratic, quadratic and linear models were \(-30.99\), \(-26.39\), \(-9.54\) and \(-6.12\), respectively. Based on these analysis results, an exponential model was selected to describe the dose-response relationship for the lifetime relative risk,

\[ \text{RR(D)} = \exp(bD). \quad (4) \]

Where \( D \) is dose in cGy. Parameter \( b \) and its standard error were estimated to be 0.00440 and 0.00001, respectively. The shape of dose-response curve for the lifetime excess mortality was convex upward (right panel of Fig. 1). Because there is a relationship between the lifetime excess mortality and the lifetime relative risk, as mentioned above (equation 2), the dose-response relationship for the lifetime excess mortality can be described by

\[ \text{EM(D)} = 1 - \exp(-bD). \quad (5) \]

The value of parameter \( b \) is the same as that in equa-

![Fig. 1. Dose-response relationship for the lifetime relative risk (left panel) and for the lifetime excess mortality (right panel) in mice irradiated in the neonatal period with gamma rays. The vertical bars represent the standard errors.](https://academic.oup.com/jrr/article-abstract/43/3/313/959008)
tion 4. The lifetime excess mortality at 1 Gy was estimated to be 0.356, which implies that 35.6% of mice irradiated neonatally with 1 Gy gamma rays died from radiation-induced causes. The life-shortening effect of 1 Gy gamma rays was estimated to be 6.7%.

Temporal pattern of manifestation

The temporal variations of the cumulative observed mortality in unirradiated and irradiated groups are summarized in Table 1. These were basic data for an analysis of the temporal pattern of manifestation of radiation-induced late effects. The mor-

| Age (days) | Dose (cGy) | 0 | 48 | 95 | 143 | 190 | 238 | 285 |
|-----------|------------|---|----|----|-----|-----|-----|-----|
| 51–250    | 0.06±0.06* | 0.22±0.16 | 0.15±0.06 | 0.15±0.15 | 0.15±0.15 | 0.07±0.04 | 1.30±0.48 |
| 251–450   | 0.28±0.13 | 1.39±0.46 | 1.53±0.48 | 1.52±0.47 | 1.74±0.65 | 3.31±0.78 |
| 451–550   | 1.26±0.38 | 2.54±0.89 | 1.57±0.70 | 4.74±1.20 | 8.97±2.08 | 7.74±1.69 |
| 551–650   | 4.57±0.72 | 6.26±1.39 | 11.7±1.9  | 13.0±2.0  | 18.3±3.1  | 14.9±2.5  |
| 651–750   | 13.0±1.2 | 21.5±2.54 | 26.6±2.9  | 31.3±3.1  | 38.4±4.7  | 50.4±4.4  |
| 751–850   | 38.9±2.1 | 61.8±4.6  | 81.2±5.8  | 87.3±8.4  | 101±129   |
| 851–950   | 68.2±3.4 | 90.5±7.3  | 129±10   | 141±14   | 169±22   | 210±23   |
| 951–1050  | 107±6   | 167±21   | 216±44   | 207±45   | 339±224  |
| 1051–1150 | 187±18  | 286±75   | 500±253  |
| 1151–1250 | 392±89  | 541±33   |

*mortality rate± standard error

| Age (days) | Dose (cGy) | 48 | 95 | 143 | 190 | 238 | 285 |
|-----------|------------|----|----|-----|-----|-----|-----|
| 51–250    | 0.16±0.17* | 0.09±0.08 | 0.10±0.16 | 0.09±0.16 | 0.68±0.42 | 1.24±0.49 |
| 251–450   | −0.06±0.20 | 1.17±0.47 | 1.25±0.49 | 1.24±0.50 | 1.46±0.66 | 3.03±0.79 |
| 451–550   | 0.50±0.73  | 1.28±0.96 | 0.31±0.79 | 3.48±1.26 | 7.71±2.21 | 6.18±1.73 |
| 551–650   | −0.20±1.21 | 1.69±1.56 | 7.13±2.01 | 8.43±2.10 | 14.2±3.2  | 10.3±2.6  |
| 651–750   | 6.50±2.36  | 8.50±2.81 | 13.6±3.1  | 18.3±3.3  | 25.4±4.8  | 37.4±4.6  |
| 751–850   | −0.50±3.74 | 22.9±5.1  | 17.5±5.0  | 42.3±6.2  | 48.4±8.6  | 62.1±8.8  |
| 851–950   | 19.1±6.4   | 22.3±8.0  | 60.8±10.5 | 72.8±14.1 | 101±22   | 142±23   |
| 951–1050  | 40.0±14.2  | 60.0±21.9 | 84.0±28.2 | 109±44   | 100±45   | 232±224  |
| 1051–1150 | −10.0±40.1 | 99.0±77.2 | 13.0±131  | 313±253  |
| 1151–1250 | 149.0±345  | 392±89    |

*absolute risk ± standard error
tality rate in each age interval is represented as the number of deaths per 10,000 mouse · day (MD) at risk, as shown in Table 2. The mortality rate increased with increasing age in the control and irradiated groups. The absolute risk, that is the difference between the mortality rate in the irradiated group and that in the control group, is shown in Table 3. The increase in the mortality rate during 51–250 days of age was statistically significant in only one group irradiated with 285 cGy (P<0.05). The mortality rate during 251–450 days of age after irradiation with 95, 143, 190, 238 or 285 cGy was significantly higher than that in the control group, but the mortality rate in the group irradiated with 48 cGy during 251–450 days of age was not dif-

Table 4. Temporal variation of the relative risk.

| Age (days) | Dose (cGy) | 48   | 95   | 143  | 190  | 238  | 285  |
|-----------|------------|------|------|------|------|------|------|
| 51–250    | 3.91±4.78* | 2.54±2.78 | 2.67±3.78 | 2.66±3.75 | 13.0±14.9 | 22.9±22.4 |
| 251–450   | 0.79±0.66  | 4.91±2.72 | 5.40±2.94 | 5.37±2.92 | 6.16±3.57 | 11.7±5.9  |
| 451–550   | 1.42±0.66  | 2.01±0.93 | 1.25±0.67 | 3.76±1.47 | 7.11±2.70 | 5.90±2.22 |
| 551–650   | 0.96±0.26  | 1.37±0.37 | 2.57±0.56 | 2.84±0.62 | 4.13±0.94 | 3.26±0.74 |
| 651–750   | 1.50±0.21  | 1.66±0.25 | 2.05±0.29 | 2.42±0.38 | 2.96±0.45 | 3.88±0.50 |
| 751–850   | 0.99±0.10  | 1.59±0.15 | 1.45±0.14 | 2.09±0.19 | 2.24±0.25 | 2.59±0.26 |
| 851–950   | 1.21±0.10  | 1.33±0.13 | 1.90±0.17 | 2.06±0.23 | 2.48±0.35 | 3.08±0.37 |
| 951–1050  | 1.37±0.14  | 1.55±0.25 | 1.78±0.28 | 2.02±0.46 | 1.92±0.43 | 3.16±0.29 |
| 1051–1150 | 0.95±0.21  | 1.53±0.48 | 1.07±0.70 | 2.68±1.38 |           |           |
| 1151–1250 | 1.38±0.09  |           |           |           |           |           |

* relative risk ± standard error

Table 5. Temporal variation of the cumulative relative risk.

| Age (days) | Dose (cGy) | 48   | 95   | 143  | 190  | 238  | 285  |
|-----------|------------|------|------|------|------|------|------|
| 250       | 3.91±3.91* | 2.54±2.78 | 2.68±2.67 | 2.65±2.65 | 13.0±12.9 | 22.9±22.9 |
| 450       | 1.31±0.74  | 4.08±2.13 | 4.95±2.45 | 2.91±2.44 | 7.30±3.53 | 13.7±6.0  |
| 550       | 1.38±0.49  | 2.75±0.93 | 2.57±0.87 | 4.18±1.28 | 7.19±2.14 | 8.73±2.42 |
| 650       | 1.10±0.23  | 1.80±0.38 | 2.56±0.48 | 3.27±0.58 | 5.14±0.92 | 6.06±0.81 |
| 750       | 1.35±0.16  | 1.71±0.21 | 2.24±0.25 | 2.74±0.30 | 3.85±0.43 | 4.36±0.45 |
| 850       | 1.14±0.08  | 1.64±0.12 | 1.80±0.13 | 2.41±0.17 | 3.06±0.25 | 3.57±0.26 |
| 950       | 1.19±0.07  | 1.54±0.09 | 1.83±0.11 | 2.33±0.14 | 2.94±0.21 | 3.49±0.22 |
| 1050      | 1.22±0.06  | 1.54±0.08 | 1.83±0.10 | 2.31±0.13 | 2.89±0.20 | 3.49±0.22 |
| 1150      | 1.20±0.06  | 1.54±0.08 | 1.81±0.10 | 2.31±0.13 |           |           |
| 1250      | 1.21±0.06  |           |           |           |           |           |

* cumulative relative risk ± standard error
different from the control rate. In the group irradiated with 48 cGy the mortality rate was higher than that in the control group during 651–750, 851–950 and 951–1050 days of age. These results showed a dose-dependent shortening of the latent period for manifesting radiation-induced lethal diseases. The absolute risk increased with increasing age (Table 3). The relationship between the absolute risk and age was concave upward in the linear scale graph, and was convex upward on semi-logarithmic scale plotting. The temporal variation of the relative risk for the mortality rate is given in Table 4. A marked decrease in the relative risk was observed in high-dose irradiated mice with increasing age. Until about age 750 days, the relative risk decreased rapidly, and thereafter decreased slowly. When mice were irradiated with 48 or 95 cGy gamma rays, the decrease in the relative risk with animal age was not prominent, although a trend of decrease was also observed.

The temporal variation of the cumulative relative risk in each irradiated group is shown in Table 5, and plotted against age in Fig. 2. The final value of the cumulative relative risk implies the lifetime relative risk. The cumulative relative risk decreased rapidly during the anterior half of life, and reached a plateau.

### Table 6. Temporal variation of the cumulative excess mortality.

| Age (days) | 48 | 95 | 143 | 190 | 238 | 285 |
|------------|----|----|-----|-----|-----|-----|
| 250        | 0.003±0.002* | 0.001±0.001 | 0.002±0.001 | 0.002±0.001 | 0.013±0.001 | 0.024±0.001 |
| 450        | 0.002±0.004 | 0.021±0.009 | 0.027±0.010 | 0.026±0.010 | 0.041±0.013 | 0.081±0.015 |
| 550        | 0.007±0.008 | 0.033±0.013 | 0.040±0.012 | 0.059±0.015 | 0.113±0.023 | 0.137±0.021 |
| 650        | 0.005±0.014 | 0.049±0.020 | 0.094±0.022 | 0.133±0.024 | 0.226±0.034 | 0.218±0.029 |
| 750        | 0.061±0.025 | 0.118±0.030 | 0.197±0.032 | 0.265±0.034 | 0.381±0.045 | 0.442±0.040 |
| 850        | 0.058±0.034 | 0.243±0.041 | 0.286±0.041 | 0.437±0.043 | 0.542±0.054 | 0.614±0.047 |
| 950        | 0.126±0.041 | 0.302±0.040 | 0.410±0.046 | 0.535±0.046 | 0.638±0.058 | 0.708±0.050 |
| 1050       | 0.170±0.044 | 0.346±0.049 | 0.446±0.048 | 0.562±0.048 | 0.654±0.058 | 0.718±0.050 |
| 1150       | 0.169±0.045 | 0.352±0.049 | 0.448±0.048 | 0.568±0.048 |              |              |
| 1250       | 0.170±0.045 |              |              |              |              |              |

* cumulative excess mortality ± standard error
in the last part of life. The temporal distribution of the excess mortality in each irradiated group, which is mortality attributable to radiation exposure, is summarized in Table 6. The cumulative excess mortalities are plotted as a function of age in Fig. 3. It was apparent that the temporal distribution of manifestation of late effects of radiation was shifted to younger ages depending on the dose of gamma rays. The shape of the cumulative distribution of excess mortality was a somewhat distorted sigmoid curve. A logistic specification was used to analyze the temporal distribution of the excess mortality. The following logistic function was fitted to the temporal distribution of the cumulative excess mortality:

$$EM(D, T) = EM(D) / (1 + \exp(p - qT)).$$ (6)

Parameters p and q were estimated as regression coefficients. The half expression time ($T_{1/2}$) of the excess mortality can be estimated using $T_{1/2} = p/q$. The values of the parameters in the irradiated groups are summarized in Table 7. Parameter p decreased with

![Fig. 3. Temporal variation of the cumulative excess mortality in mice irradiated at the neonatal period with gamma rays. The numerical characters in the figure represent the doses of gamma rays in cGy.](image)

**Table 7.** Parameters p and q of the logistic function for the distribution of excess mortality.

| Dose (cGy) | Parameter p ($\pm$SE*) | Parameter q ($\pm$SE*) | Half expression time (days±) |
|------------|-------------------------|-------------------------|-----------------------------|
| 48         | 10.54±1.94               | 0.0122±0.0026           | 861.7                       |
| 95         | 8.42±0.71                | 0.0105±0.00098          | 799.2                       |
| 143        | 7.51±0.64                | 0.00967±0.00091         | 777.0                       |
| 190        | 8.24±0.31                | 0.01095±0.00045         | 752.3                       |
| 238        | 7.22±0.34                | 0.01018±0.00054         | 708.6                       |
| 285        | 6.43±0.65                | 0.00911±0.00100         | 706.7                       |

* SE: standard error
increasing dose of gamma rays, which indicates a
dose-dependent shortening of the latent period for the
expression of excess mortality. The rate coefficient for
the decrease in parameter p of the logistic function
was estimated to be 13.55% per Gy, with a standard
error of 2.77% per Gy. Also, parameter q of the logis-
tic function decreased with increasing dose. This
result indicates that the distribution became wider with
increasing dose. The half-expression time of the
excess mortality was shortened depending on the dose
of the gamma rays.

DISCUSSION

The present study showed a dose-response rela-
tionship for the lifetime excess mortality after irradia-
tion in the neonatal period of mice. The lifetime
excess mortality was calculated based on a self-
explanatory assumption that any increase in the mor-
tality rate is attributable to radiation exposure. The
lifetime excess mortality of ionizing radiation in the
human population is estimated by projection models
based on data sets from epidemiological investiga-
tions. In life span studies using laboratory animals, the
lifetime excess mortality can be obtained directly, as
described here. The shape of the dose-response rela-
tionship for the lifetime excess mortality was convex
upward, which is consistent with the results of a pre-
vious study (Sasaki, 1992)\textsuperscript{23}. On the other hand, the
dose-response relationship for the lifetime relative risk
was concave upward, which is an alternative compre-
hensive measure of the lifetime risk of exposure to
radiation. However, these results are not contradictory,
because there is a relationship between the lifetime
excess mortality and the lifetime relative risk, as
described in equation 2. The non-linearity of the dose-
response relationship for the lifetime excess mortality
may be a common characteristic. UNSCEAR 1994
report\textsuperscript{19} recognised a non-linearity of the lifetime risk,
which corresponds to the lifetime excess mortality in
the present paper. The lifetime risks at 1 Sv and 0.2 Sv
are given in the UNSCEAR report. Simple linear
extrapolation from values at 1 Sv underestimates the
values at 0.2 Sv by 10–20%.

Prentice \textit{et al.} (1982) examined the dose-mortal-
ity relationship in RFM mice irradiated in the young
adult period with gamma rays using the proportional
hazard method, and concluded that the lifetime rela-
tive risk for the overall mortality rate is a valuable
parameter to estimate the risk of low-dose radiation\textsuperscript{20}).
The lifetime excess mortality after irradiation with 1
Gy gamma rays in the neonatal period of mouse was
estimated to be 35.6%. This value is not inordinately
high, because mice of the neonatal period are highly
susceptible to the induction of several types of solid
tumors, as shown in our previous studies\textsuperscript{24,26–28}). We
examined the age-dependence of susceptibility for the
lifetime relative risk, and showed that mice in the neo-
natal-to-puberty period are most susceptible\textsuperscript{23}). The
shape of the dose-response relationship and age-
dependence of susceptibility for the lifetime excess
mortality may be common beyond a difference of ani-
mal species.

It became evident that there was a remarkable
decrease in the relative risk with increasing age after
irradiation during the neonatal period of mice. The
decrease in the relative risk of solid cancer was also
observed among atomic bomb survivors exposed dur-
ing childhood period\textsuperscript{18,29} and individuals exposed to
medical radiation in childhood\textsuperscript{30}), whereas it has been
reported that the relative risk for solid cancer remains
constant among the atomic bomb survivors exposed
during adulthood\textsuperscript{18,29}). It should be noted, however,
that the probability of death in irradiated groups was
persistently higher than the background rate through-
out life. The absolute risk increased with increasing
time. These results indicated that the constant relative
risk model and absolute risk model cannot adequately
describe the temporal pattern of manifestation of radi-
ation-induced long-term effects for neonatal exposure.
We analysed the distribution of the excess mortality by
fitting a logistic function, and showed that the latent
period became shorter and the distribution became
wider after irradiation during the neonatal period,
depending on the dose of gamma rays. The magnitude
of the excess mortality and its temporal distribution
are well described by equations 5 and 6. The majority
of the excess mortality in the present study may be due to late-occurring lethal diseases other than lymphohematopoietic tissue neoplasms. Myeloid leukemia could not be induced by irradiation in the neonatal period of mice. B6C3F1 mice were shown not to be highly susceptible for the induction of thymic lymphoma by radiation. In the present experiment the incidence of thymic lymphoma in the group irradiated with 2.85 Gy (2.9%) was significantly higher than that in the control group (0.3%), but no statistically significant difference was detected in other irradiated groups. When lymphohematopoietic tissue neoplasms develop substantially, the temporal distribution of these neoplasms should be analysed separately from that for late-occurring lethal diseases.

The present study clearly showed that the essential feature of the long-term effects of radiation is a persistent increase in the mortality rate. The mortality rate increased exponentially with increasing dose of gamma rays. The exponential increase in the mortality rate resulted in a dose-linear shortening of the mean life span. The lifetime excess mortality may be an excellent comprehensive measure of the long-term effects of radiation. Using these comprehensive measures we are attempting to analyze the long-term effects of lower doses of radiation delivered during a neonatal period of mice.

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REFERENCES

1. Henshaw, P. S. (1944) Experimental roentgen injury. IV. Effects of repeated small doses of x-rays on blood picture, tissue morphology, and life span in mice. J. Natl. Cancer Inst. 4: 513–522.
2. Upton, A. C. (1957) Ionizing radiation and the aging process. A review. J. Gerontol. 12: 306–313.
3. Storer, J. B. and Sanders, P. C. (1958) Relative effectiveness of neutrons for production of delayed biological effects. I. Effect of single doses of thermal neutrons on life span of mice. Radiat. Res. 8: 64–70.
4. Comfort, A. (1959) Natural aging and the effects of radiation. Radiat. Res. Suppl. 1: 216–234.
5. Mole, R. H. (1959) Some aspects of mammalian radiobiology. Radiat. Res. Suppl. 1: 124–148.
6. Lindop, P. J. and Rotblat, J. (1961) Long-term effects of a single whole-body exposure of mice to ionizing radiations. II. Causes of death. Proc. Royal Soc. London Ser. B 154: 350–368.
7. Lindop, P. J. and Rotblat, J. (1962) The age factor in the susceptibility of man and animals to radiation. Brit. J. Radiol. 35: 23–31.
8. Walburg, H. E. Jr. (1975) Radiation-induced life shortening and premature aging. Adv. Radiat. Biol. 5: 145–179.
9. United Nations Scientific Committee on the Effects of Atomic Radiation (1982) Ionizing Radiation: Sources and Biological Effects. Report to the General Assembly with Annexes. United Nations, New York.
10. Shimizu, Y., Kato, H., Schull, W. J. and Hoel, D. G. (1992) Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-1985: Part 3. Noncancer mortality based on the revised doses (DS86). Radiat. Res. 130: 249–266.
11. Shimizu, Y., Pierce, D. A., Preston, D. L. and Mabuchi, K. (1999) Studies of the Mortality of Atomic Bomb Survivors. Report 12, Part II. Noncancer Mortality: 1950-1990. Radiat. Res. 152: 374–389.
12. Sasaki, H., Kodama, K. and Yamada, M. (1991) Aging. J. Radiat. Res. 32 Suppl. 1: 310–326.
13. Maisin, J. R., Wamberse, A., Gerber, G. B., Matteelin, G., Lambiet-Collier, M. and Gueulette, J. (1983) The effects of a fractionated gamma irradiation on life shortening and disease incidence in BALB/c mice. Radiat. Res. 94: 359–373.
14. Maisin, J. R., Wambersie, A., Gerber, G. B., Matteelin, G., Lambiet-Collier, M. and Gueulette, J. (1988) Life-shortening and disease incidence in C57Bl mice after single and fractionated γ and high-Energy neutron exposure. Radiat. Res. 113: 300–317.
15. Phemister, R. D., Thomassen, R. W., Norrdin, R. W. and Iaenke, R. S. (1973) Renal failure in perinatally irradiated beagles. Radiat. Res. 55: 399–410.
16. Benjamin, S. A., Lee, A. C., Angleton, G. M., Saunders, W. J., Keefe, T. J. and Mallinckrodt, C. H. (1998) Mortality in Beagles Irradiated during Prenatal and Postnatal Development. 1. Contribution of Non-neoplastic Dis-
17. National Academy of Sciences, Committee on the Biological Effects of Ionizing Radiations (1990) Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V). National Academy Press, Washington, DC.

18. Pierce, D. A., Shimizu, Y., Preston, D. L., Vaeth, M. and Mabuchi, K. (1996) Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–990. Radiat. Res. 146: 1–27.

19. United Nations Scientific Committee on the Effects of Atomic Radiation (1994) Sources and effects of ionizing Radiation. Report to the General Assembly with Annexes. United Nations, New York.

20. Prentice, R. L., Peterson, A. V. and Marek, P. (1982) Dose-Mortality Relationships in RFM Mice following $^{137}$Cs $\gamma$-Ray Irradiation. Radiat. Res. 90: 57–76.

21. Storer, J. B., Mitchell, T. J. and Fry, R. J. M. (1988) Extrapolation of the relative risk of radiogenic neoplasms across mouse studies and man. Radiat. Res. 114: 331–353.

22. Carnes, B. A., Olshansky, S. J. and Grahn, D. (1998) An Interspecies Prediction of the Risk of Radiation-Induced Mortality. Radiat. Res. 149: 487–492.

23. Sasaki, S. (1992): Influence of dose and age at radiation exposure on attributable risk in mice. Proceedings of International Congress on Radiation Effects and Protection, pp. 223–228, Japan Atomic Energy Research Institute.

24. Sasaki, S. and Fukuda, N. (1999) Dose-response relationship for induction of solid tumors in female B6C3F1 mice irradiated neonatally with a single dose of gamma rays. J. Radiat. Res., 40: 229–241.

25. Akaike, H. (1974) A new look at the statistical model identification. IEEE Transact. Automat. Contr. AC19: 716–723.

26. Sasaki, S. and Kasuga, T. (1981) Life shortening and carcinogenesis in mice irradiated neonatally with X rays. Radiat. Res. 88: 313–325.

27. Sasaki, S. (1991) Influence of the Age of Mice at Exposure to Radiation on Life-Shortening and Carcinogenesis. J. Radiat. Res. 32 Suppl. 2: 73–85.

28. Sasaki, S. (1991) Age-dependence of susceptibility to carcinogenesis by ionizing radiation in mice. Radiat. Environ. Biophys. 30: 205–207.

29. Shimizu, Y., Kato, H. and Schull, W. J. (1990) Studies of the mortality of A-bomb survivors. Report 9. Mortality, 1950-1985: Part 2. Cancer mortality based on the recently revised (DS86). Radiat. Res. 121: 120–141.

30. Little, M. P., Hawkins, M. M., Shore, R. E., Charles, M. W. and Hildreth, N. F. (1991) Time variations in the risk of cancer following irradiation in childhood. Radiat. Res. 126: 304–316.

31. Upton, A. C., Odell, T. T. Jr. and Sniffen, E. P. (1960) Influence of age at time of irradiation on induction of leukemia and ovarian tumors in RF mice. Proc. Soc. Exp. Biol. Med. 104: 769–772.

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