Review

Cancer Risk Associated with Low-dose and Low-dose-rate Ionizing Radiation Exposure

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Whether chronic exposure has an cancer risk per dose different from that of acute exposure is a topic of debate. This paper discusses the effect of dose rate on the strength of relationship between cancer risk and external exposure to low-LET (Linear Energy Transfer) ionizing radiation (such as X-rays and gamma rays), by reviewing important epidemiological studies. The study of atomic-bomb survivors, who had acute exposure mainly to low-LET ionizing radiation, has shown that the excess relative risk per gray (ERR/Gy) of leukemia increases in a linear-quadratic manner with an increase of radiation dose. The estimate of ERR/Gy for medium-high dose ranges was shown to be approximately two-fold larger than that for a low-dose range in the atomic-bomb survivor study. The estimate of ERR/Gy associated with acute exposure appears to be larger than those obtained from the studies of low-dose-rate exposure. On the other hand, the risk of solid cancer (or all cancers excluding leukemia) showed a linear dose-response relationship. Regarding the risk modification by dose rates, lower dose-rate exposure to high LET radiation is suspected to be associated with a larger risk. In the case of low-LET exposure, however, the cancer incidence study of residents in high natural background radiation areas of Karunagappally Taluk in Kerala State, India suggests that the ERR per dose for solid cancer after chronic radiation exposure is significantly lower than that associated with acute exposure such as that experienced by atomic-bomb survivors.

Key words: cancer risk, low-level radiation exposure

Introduction

Regarding the association of ionizing radiation exposure with cancer risk, Brenner et al. described as follows: “For X- or gamma-rays, good evidence of an increase in risk for cancer is shown at acute doses >50 mSv, and reasonable evidence for an increase in some cancer risks at doses above approximately 5 mSv. As expected from basic radiobiology (1), the doses above which statistically significant risks are seen somewhat higher for protracted exposures than for acute exposures; specifically, good evidence of an increase in some cancer risks is shown for protracted doses >100 mSv, and reasonable evidence for an increase in cancer risk at protracted doses above approximately 50 mSv” (2).

This paper discusses the effect of dose rate on the magnitude of relationship between cancer risk and external exposure to low-LET (Linear Energy Transfer) ionizing radiation (such as X-rays and gamma rays), by reviewing important epidemiological studies. The study of atomic-bomb survivors has shown that the excess relative risk per gray (ERR/Gy) of leukemia increases in a linear-quadratic manner with an increase of radiation dose, and the ERR per dose associated with low-dose exposure is lower than that for medium-high doses (3,4). On the other hand, the ERR/Gy of solid cancer risk increases linearly with radiation dose. Interestingly, a recent mortality study of atomic-bomb survivors, reported by Ozasa and his colleagues, showed that the dose response curve of solid cancer was linear quadratic in the dose range of <2 Gy (3). Their finding supports the hypothesis that the dose-response is sigmoidal, which is considered to be in line with known mechanisms of carcinogenesis by some researchers (5), since the exclusion of a relatively high dose range from a sigmoidal dose-response will make it linear quadratic. It should be noted, however, that distally exposed survivors, whose doses were estimated to be approximately zero, had about 5% higher cancer rates than estimated for zero dose from proximally exposed survivors (6). Their finding suggests a possibility that distally and proximally exposed groups are different in their lifestyles and exposure to environmental factors. The exclusion of those distally exposed from analysis is likely to make the dose response curve more linear.

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The widely accepted definitions of low and high dose-rates are the dose-rate below 0.1 mGy per minute and 0.1 Gy per minute or larger, respectively (7). In this paper, dose rates between the low and high dose rates will be referred to as the medium dose rate. By far the most important study on the cancer risk associated with acute exposure is the follow-up study of atomic bomb survivors. In the case of low-dose-rate exposure, its association with cancer risk is not entirely clear. Let alone the dose-response relationship between cancer risk and radiation exposure. Most of epidemiological studies on low dose rates have relatively low cumulative doses, making it difficult to evaluate radiation-related risk since such evaluation requires a long-term follow-up of a large population. Note also that there are many risk factors, such as smoking, that are much more strongly associated with cancer risk when compared with low-dose radiation exposure (8,9), and that even a weak association of those factors with radiation doses can confound the relationship between radiation exposure and cancer risk. Important epidemiological studies for evaluating the cancer risk associated with relatively low-dose-rate exposure include those on residents in high natural background radiation (HNBR) areas and in the places where the radiation levels of man-made origin have been relatively high for prolonged periods in addition to studies on nuclear workers.

### Leukemia Risk

The dose-response relationship between leukemia incidence and radiation dose among atomic-bomb survivors is known to be linear quadratic. In a recent cancer mortality study among atomic-bomb survivors, the ERR for leukemia was estimated to be 3.1 at 1 Gy and 0.15 at 100 mGy (3). Since an ERR of 0.15 at 100 mGy corresponds to the ERR of 1.5 at 1 Gy, the ERR associated with low doses is about half of that at 1 Gy.

The meta-analysis of risk conducted by Daniels and Schubauer-Berrylan showed that protracted exposure to low-dose gamma-ray radiation gave an ERR of 0.19 (95% CI: 0.07, 0.32) at 100 mGy (10) for leukemia excluding chronic lymphocytic leukemia (CLL). — CLL was excluded since this subtype of leukemia is considered not related to radiation (recent studies suggest an association though). — This value is similar to the estimate obtained from the study of atomic-bomb survivors (3,4). Similar estimates were also reported by the IARC 3-country study (11) and the IARC 15-country study (12,13), which reported the ERRs at 100 mGy of 0.22 (90% CI: 0.01, 0.57) and of 0.19 (95% CI: < 0, 0.85), respectively. In those studies, study groups led by the International Agency for Research on Cancer (IARC) conducted pooled analyses of nuclear worker data obtained from three countries (the U.S., the U.K. and Canada), and 15 countries, including those three countries, respectively. Recently, Daniels et al. conducted a pooled analysis of leukemia data among U.S. nuclear workers.

#### Table 1. Excess relative risk at 100 mGy for non-CLL leukemia studies

<table>
<thead>
<tr>
<th>Mean dose</th>
<th>Cases</th>
<th>ERR at 100 mGy</th>
<th>Authors; year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karunagappally residents, incidence, 1990–2005</td>
<td>161 mGy</td>
<td>20</td>
<td>0.372 (95% CI: &lt;0, 33.68)</td>
</tr>
<tr>
<td>Tech River residents, mortality, 1950–1999</td>
<td>300 mGy</td>
<td>49</td>
<td>0.65 (95% CI: 0.18, 2.4)</td>
</tr>
<tr>
<td>US nuclear workers, pooled analysis</td>
<td>26.5 mGy</td>
<td>264</td>
<td>0.09 (95% CI: −0.17, 0.65)</td>
</tr>
<tr>
<td>US Rocky Flats facility workers, mortality, 1952–1983</td>
<td>41 mSv</td>
<td>53</td>
<td>−0.72 (90% CI: &lt;0, 4.2)</td>
</tr>
<tr>
<td>U.S. Nuclear Power Plants, mortality, 1979–1997</td>
<td>25.7 mGy</td>
<td>26</td>
<td>0.567 (95% CI: −0.256, 3.04)</td>
</tr>
<tr>
<td>US Rocketdyne workers, mortality, 1948–2008</td>
<td>13.5 mSv</td>
<td>159</td>
<td>0.06 (95% CI: −0.50, 1.23)</td>
</tr>
<tr>
<td>U.K. National Registry for Radiation Workers, incidence, –2001</td>
<td>24.9 mSv</td>
<td>234</td>
<td>0.178 (90% CI: 0.017, 0.436)</td>
</tr>
<tr>
<td>France, COGEMA, mortality 1950–1994</td>
<td>21.7 mSv</td>
<td>57</td>
<td>0.878 (90% CI: 0.01, 2.631)</td>
</tr>
<tr>
<td>France, EDF, mortality 1961–2003</td>
<td>21.5 mSv</td>
<td>13</td>
<td>−0.68 (90% CI: −0.99, 0.94)</td>
</tr>
<tr>
<td>Japanese nuclear workers 1991–2002</td>
<td>12.2 mSv</td>
<td>80</td>
<td>−0.193 (95% CI: −0.612, 0.857)</td>
</tr>
<tr>
<td>Mayak workers, mortality –1997</td>
<td>810 mGy</td>
<td>66</td>
<td>0.099 (90% CI: 0.045, 0.212)</td>
</tr>
<tr>
<td>Ukrainian Chernobyl workers, incident cases in, 1986–2006</td>
<td>81.3 mGy</td>
<td>52</td>
<td>0.221 (95% CI: 0.005, 0.761)</td>
</tr>
<tr>
<td>Chernobyl clean-up workers, incident cases in Russia (1993–1998), Belarus (1993–2000) and Baltic countries (1990–1998)</td>
<td>12.8 mGy</td>
<td>19</td>
<td>0.50 (90% CI: −0.38, 5.70)</td>
</tr>
</tbody>
</table>

*The Japanese study includes CLL. In this country CLL is uncommon. Red bone marrow dose was used for risk analysis. *The study population consisted of workers who were employed at the Hanford Site, the Savannah River Site, the Oak Ridge National Laboratory, the Los Alamos National Laboratory, including the Zia Company employees, the Idaho National Laboratory, and the Portsmouth Naval Shipyard. COGEMA: Compagnie générale des matières nucléaires. In 2001, Cogema was merged with Framatome and CEA (Commissariat à l’énergie atomique et aux énergies alternatives) Industrie to form the larger group Areva. EDF: Electricité de France, an electric utility company in France. A case-control study nested in a cohort (the mean dose is that in controls). The dose units for mean doses are those used in the original paper. In the U.K. National Registry for Radiation Workers, follow-up was lagged by two years. In the study Russian, Beralus and Baltic Chernobyl clean-up workers, dose or follow-up was not lagged. In the rest of studies, dose was lagged by two years.
workers (14). They reported an adjusted ERR of 0.09 (95% CI: −0.17, 0.65) per 100 mGy for non-CLL leukemia.

Table 1 summarizes ERR at 100 mGy for non-CLL leukemia. The studies listed in this table cover all the major studies included in the meta-analysis of Daniels and Schubauer-Berigan (10) with the number of cases 10 or larger. Exceptions are the IARC 15-country study (12) and Canadian studies. The IARC study was excluded in order to avoid overlap of studies. However, all the large-scale studies included in that study are included in Table 1. Canadian studies were excluded since they used the National Dose Registry (NDR). Problems involved in the NDR will be discussed later. The study on Ukrainian Chernobyl clean-up workers was replaced by a recently reported study of Chernobyl liquidators of Ukraine (26). Yangjiang study was excluded since confidence interval could not be estimated. The meta-analysis using rmeta package of R software gave a summary ERR at 100 mGy of 0.09 (95% CI: −0.03, 0.2, estimated heterogeneity of variance = 0.99). This estimate is significantly smaller than 3.1 at 1 Gy reported by the atomic-bomb survivor study (P = 0.017). It should be noted, however, that this comparison does not take into account the time since exposure, which strongly affects ERR per unit dose (4).

Taken together, the estimate of ERR/Gy for leukemia in medium to high dose ranges is approximately two-fold larger than that for a low-dose range, and appears to be larger than those obtained from the studies of low-dose-rate exposure.

Solid Cancer Risk

Solid cancer is a collective term for cancers excluding leukemia and lymphoma. In this paper, we use the terms of “solid cancers” and “cancers excluding leukemia” interchangeably.

Studies in high natural background radiation areas: A workshop entitled “International Review Meeting on Low Dose Rate Radioepidemiology of High Background Radiation Areas”, was held on January 15–16, 2010, Tokyo, Japan (28). After reviewing epidemiological studies of residents in two HNBR areas, the Karunagappally study in India and the Yangjiang study in China, the reviewers, including John Boice and Jolyon Hendry, concluded as follows: “Discussions at this workshop highlighted the unique opportunity to obtain quantitative information on the long-term effects of radiation doses delivered over protracted periods at a low rate but cumulating to relatively high levels. Populations residing in areas of high background radiation, particularly in India, represent a large and relatively unrecognized database whose value is just emerging. Lifetime doses can be accurately estimated for large numbers of individuals, cancer incidence can be determined, confounding factors can be adjusted for in the analyses, the cumulative doses can reach levels approaching 1 Gy with substantial numbers exceed 500 mGy, the studies are larger and doses greater than current studies of occupational and environmental populations (29).”

The coastal belt of Karunagappally Taluk (an administrative division) is known for HNBR from thorium-containing monazite sand. Among 12 panchayats (an administrative unit, literally means assembly) in this taluk, several coastal panchayats have medium outdoor radiation doses of more than 4 mGy per year. In certain locations on the coast, it is as high as 70 mGy per year. A cohort of all residents in Karunagappally Taluk (population size: 385,103 according to the population census conducted in 1990) was established in the 1990s to evaluate health effects of HNBR (15). For radiation risk analysis, six panchayats, including two panchayats with relatively low environmental doses, in coastal areas were chosen. The radiation subcohort consists of 173,067 residents, and cancer incidence among residents aged 30–84 years in this subcohort (N = 69,958) was analyzed. Cumulative radiation doses, lagged by 2 years for leukemia and 10 years for cancer excluding leukemia, were estimated for each individual, using outdoor and indoor doses of each household, and sex- and age-specific house occupancy factors. Following 69,958 residents for 10.5 years on average, 736,586 person years of observation were accumulated, and 1,379 cancer cases including 30 cases of leukemia were identified by the end of 2005. Poisson regression analysis of cohort data, stratified by sex, attained age, follow-up intervals, socio-demographic factors and bidi smoking, showed no excess cancer risk from exposure to terrestrial gamma radiation. The ERR/Gy of cancer excluding leukemia, assuming a linear dose-response relationship, was estimated to be −0.13 (95% CI: −0.58, 0.46). In site-specific analysis of solid cancers, no cancer site was significantly related to cumulative radiation dose.

Yangjiang area in Guandong Province, China, is also known for its HNBR. Most of the inhabitants have lived in the study areas for 6 or more generations (30). The average annual doses of external radiation from the natural sources, including thorium, in the HNBR area and in the control area were estimated to be 2.10 and 0.77 mSv per year, respectively (31,32). The prevalence of thyroid nodules in HNBR areas was similar to that in the control area (33). The frequency of stable-type chromosome aberrations in peripheral lymphocytes was 0.29 (per 100 metaphases) in the HNBR area and was 0.18 in the control area; and the frequency of unstable-type chromosome aberrations was 0.16 in the HNBR area and was 0.06 in the control area (33). Recent chromosome studies in Yangjiang showed that the cumulative HNBR dose was significantly related to the frequencies
of unstable-type chromosome aberrations (34) but not to that of stable-type aberrations (35,36).

Tao et al. analyzed the data obtained from the follow-up of a cohort of 31,604 men and women aged 30–74 living in Yangjiang area during the period 1979–1998 (37). Cumulative external radiation dose, lagged by 2 years for leukemia and 10 years for cancer excluding leukemia, was estimated for each individual based on hamlet-specific indoor and outdoor doses, and sex- and age-specific house occupancy factors. The follow-up study accumulated 736,942 person-years at risk, and ascertained 6,005 deaths, including 956 cancer deaths (14 deaths of leukemia). Mean cumulative radiation doses from natural radiation in the HNBR and control area residents were 84.8 mGy and 21.6 mGy, respectively. The ERR/Gy of cancer excluding leukemia was estimated to be $-1.01 (95\% CI: -2.53, 0.95)$. In site-specific analysis, liver-cancer mortality was inversely related to the cumulative dose ($P=0.002$). Since mortality of liver diseases other than cancer tended to increase with cumulative radiation dose ($P=0.061$), misdiagnosis between liver cirrhosis and liver cancer was suspected. When cancer of the liver and leukemia were excluded from all cancers, the ERR/Gy was 0.19 (95\% CI: $-1.87, 3.04$).

Other studies of residents chronically exposed: In addition to the studies of HNBR area residents in India and China, there are at least a few important studies on residents exposed to protracted radiation exposure. They are the studies of residents along the Techa River, which runs through areas east to the Ural mountains in central Russia (38,39), and of Taiwan building residents exposed to radiation from $^{60}$Co (40).

Between 1949 and 1956, 114 PBq of radionuclides were discharged into the Techa River from the Mayak Production Association. In 1951, the largest amount of radioactive waste was released into the environment (41). The nearest settlement on the Techa River to the site of releases (7 km downstream) was Metlino, which was situated on the shore of reservoir R-4. Dose rates from external exposure in the gardens of this town along the shore were estimated to be 30–100 microR/s in August 1951. During the period 1949–1951, the Metlino population had an average dose of about 2 Sv from the external exposure (42). To examine the health effects among residents, a cohort of residents (the Extended Techa River Cohort) who lived along the Techa River during the period between 1950 and 1960 was established. According to the report by Krestinina et al. (38), 18,389 people were residents of one of the 25 villages in Chelyabinsk Oblast (7–148 km from the release point) and 11,411 people were those who lived in one of the 16 riverside villages in Kurgan Oblast (155–237 km from the release point). It is known that a sizable number of cohort members were those who were relocated away from the upper Techa River in the 1950s.

Data on solid cancer cases have been available since 1956, when local health authorities started to request physicians to report cancer cases to the regional oncological center. Cancer incidence data are available for a subcohort consisting of the 17,433 cohort members who had lived in the original catchment areas, which are Chelyabinsk City and five raions of Chelyabinsk Oblast. In a cancer incidence study that ascertained 1,836 solid cancer cases during the period 1956–2002, an ERR estimate of 0.99/Gy (95\% CI: 0.3, 1.9) was obtained, assuming a linear dose-response relationship. This study used the doses estimated by Techa River Dosimetry System (TRDS) 2000 (41). Recently, the results of mortality study using individual dose estimates calculated by the latest dosimetry system, TRDS-2009, were published (39). In this study, 2,303 solid cancer deaths were ascertained during the period between 1950 and 2007. Poison regression analysis of solid cancer gave an ERR/Gy of 0.61 (95\% CI: 0.04, 1.27). This estimate is similar to the one observed in the atomic-bomb survivor study. A possible explanation for this finding is that medium-dose-rate exposure may give an ERR per dose similar to that associated with acute exposure. Note that the dose rates of radiation exposure in the ETRC include the medium range. However, it should also be pointed out that the observed ERR estimate was not significantly different from the estimates obtained from the atomic-bomb survivor study or the Karunagappally study in India. Its wide confidence interval precludes us from drawing any definitive conclusions.

One of the major limitations of the study is the lack of information on lifestyles. It should be noted that the lifestyles of residents are likely to have changed after relocation, which tended to start earlier in areas with higher radiation doses (43). Loss to follow-up, largely due to migration, is another limitation of this study (39).

In Taiwan, more than 200 buildings, including dozens of school complexes, built in 1983 and 1984 were found to have higher than normal indoor radiation levels. An investigation found that reinforcing rods were manufactured from Cobalt-60 contaminated steel billets, which were produced in at least one steel mill in northern Taiwan in late 1982. Occupants were estimated to have been exposed to radiation dose rates of 0.5 to 270 $\mu$Gy/h. A follow-up of 6,242 residents, who had a cumulative dose of 48 mGy on average, ascertained 117 cancer cases during the period between 1983 and 2005. The study obtained an ERR of 0.2/Gy (90\% CI: $-0.5, 0.8$) for all cancers excluding leukemia (40). Note, however, that confounding, in particular by smoking, may have inflated the radiation risk since the lung cancer had an ERR estimate of 0.9/Gy, which was much larger than those of other cancers. It should also be
pointed out that, due to its wide confidence interval, the observed ERR estimate was not significantly different from the estimates obtained from the atomic-bomb survivor study or the Karunagappally study in India.

Soviet nuclear weapons testing at the Semipalatinsk nuclear test site, Kazakhstan caused external and internal environmental exposures to residents in its vicinity. A historical cohort of 19,545 inhabitants with doses ranging from 20 mSv to 4 Sv was established. The first analysis of cancer mortality data obtained from the follow-up of the cohort during the period 1960–1999 gave an ERR/Sv of 1.77 (95% CI: 1.35, 2.27) for solid cancer (44). Since authors concerned a lack of comparability between the exposed and control groups, they excluded the control group, and calculated an ERR. The estimate of ERR/Sv of solid cancer became 0.81 (95% CI: 0.46, 1.33) after such an exclusion. It should be noted that the involvement of confounding factors in risk estimation cannot be denied. For example, esophagus cancer death, which accounted for 36% (317/889) of all solid tumor deaths in this study, had RRs of 4.45 and 3.12 for dose categories of 500− and 750+ mSv, respectively. Together with a relatively large RR of 5.68 for lung cancer in the dose category of 750+ mSv, those observations suggest a possible confounding by smoking. Note also that this is the only study showing an evident cancer risk increase among residents exposed to radioactive fallout. Further studies taking into account potential confounding factors seem necessary.

Nuclear worker study: The cancer risk of chronic radiation exposure has also been examined by epidemiological studies of nuclear workers. By far the most extensive evaluation of solid cancer risk among nuclear worker is the IARC 15-country study (12). This study analyzed the pooled data of 407,391 workers individually monitored for external radiation, and the follow-up accumulated a total of 5.2 million person years with the total collective recorded doseof 7,892 Sv. This study showed a statistically significant excess of all cancers excluding leukemia (5,024 deaths) in relation to occupational radiation exposure: the ERR/Gy was 0.97 (95% CI: 0.14, 1.97), which is much larger than the estimate (= −0.07; 90% CI: −0.4, 0.3) reported by IARC’s 3-country study (11). Note that medical exposure, which could be relatively large among nuclear workers, could not be taken into account in this study.

The validity of the radiation risk estimates reported by the IARC 15-country study has been questioned (45,46). For example, smoking might have confounded the results. In addition, Canadian data used in their risk estimation gave an ERR estimate of 6.65 (90% CI: 2.56, 13.0) for all cancers excluding leukemia. This anomalously large radiation-associated risk is suspected to be related to missing dosimetry information, which occurred when dosimetry data were transferred from the AECL (Atomic Energy Canada Limited) worker records to the NDR (47). Canadian Nuclear Safety Commission (CNSC) reanalyzed the cancer mortality data and concluded as follows: “a group of 3,088 nuclear energy workers at AECL first employed before 1965 (1956–1964) was the only group of workers with a consistent radiation-associated increase in risk of solid cancer mortality (48). The risk estimate was statistically significant and was nine times higher than the risk estimates for workers with zero dose. This group of AECL nuclear energy workers had a profound impact on the Canadian and 15-country study findings.” “Despite this apparent increase in cancer risk among early AECL nuclear energy workers, a comparison using the Canadian Mortality Database showed statistically significant lower rates of all causes of death and cancer mortality for this group than for the general Canadian population. This fact reinforces CNSC concerns that there remains a data problem as opposed to a true increase in their risk of solid cancer mortality.”

Akiba and Mizuno (24) conducted a meta-analysis of all cancers excluding leukemia or solid cancer reported by mortality follow-up studies of nuclear workers in order to make a comparison between Japanese nuclear workers and those in other countries. Their meta-analysis included the most recent publications of all the nuclear-worker studies with 100 or more cancer deaths that reported the estimate of ERR per dose for all cancers excluding leukemia (or solid cancer). The smaller studies were not included since they are too small to make significant contribution to the composite estimate. For Canadian data, they used the report of Gribbin et al. since it was the last Canadian nuclear-worker study that did not use the NDR data (49). The Mayak study was excluded since the dose from internal exposure dose is large (25). Their meta-analysis used the risk estimates reported by eight studies with 14,208 cancer deaths in total, which is nearly three times larger than that of all cancers excluding leukemia used in the standard analysis of IARC’s 15-country study. The summary estimate of ERR/Sv was 0.14 (95% CI: −0.12, 0.41). This estimate could have been even lower if the Mayak study was included, which reported an ERR of 0.08/Gy for all cancers other than leukemia after excluding cancers of the lung, liver, and skeletons, to which internal exposure made a significant contribution (24).

Comparison of risks per dose between acute and chronic exposure studies: Here, the ERR per dose of cancers excluding leukemia reported by the Karunagappally study, which examined the cancer risk of chronic exposure, is compared with that cancer risk obtained in the atomic-bomb survivor study, the single most important study for acute exposure. The cancer incidence data of atomic-bomb survivors are those available at the website of RERF. Preston et al. reported an
ERR/Gy estimate of 0.47 for those exposed at age 30 and attained age of 70 (50). In the case of Karunagappally study, the average attained age was 57.7 years. Since Karunagappally residents were exposed to natural radiation continuously, it is difficult to determine age at exposure. If the average age at exposure is assumed to be the half of average attained age, it will be 28.8 years. In the atomic bomb survivor data, the estimate of ERR/Gy for those with attained age of 57.7 and age at exposure of 28.8 was 0.649 (SE = 0.053). When this value was compared to the estimate obtained from the Karunagappally study (= -0.13), the difference between the two studies was statistically significant (P = 0.011). When the average ages at exposure are assumed to be one third and two thirds of the average attained age, the estimates of atomic bomb survivors were 0.776 (SE = 0.057) and 0.542/Gy (SE = 0.067), respectively. The corresponding P values for the difference between the Karunagappally study and the atomic-bomb survivor study were 0.003 and 0.029.

As already described in the previous paragraph, the ERR/Gy estimate reported by Preston et al. was for those exposed at age 30 and attained age of 70 (50). Without those age constraints, the estimate became 0.62 (95% CI: 0.53, 0.70). The average age at the time of bombing and the attained age were 28.0 years and 59.2 years, respectively. This average attained age is similar to that of the Karunagappally study. Next, we conducted Poisson regression analysis of atomic-bomb survivor data, using i) dose-category specific mean doses, and ii) observed and expected cancer cases, which are shown in the upper panel of Table 2. This approach gave an ERR estimate for solid cancer of 0.62 (95% CI: 0.54, 0.70). A similar analysis of Karunagappally study data (15), which are shown in the lower panel of Table 2, gave an ERR estimate for cancers excluding leukemia of -0.12. This value is quite similar to the ERR/Gy estimate of -0.13, which was reported by Nair et al. The difference of ERR/Gy between the atomic-bomb survivor study and the Karunagappally study was statistically significant (P = 0.011).

In additional analyses using the data of the Yangjiang study (37), the P value for the comparison between the Karunagappally study and the Yangjiang study (data not shown in the table) vs atomic bomb survivor study was not much different from the one obtained from the comparison between the Krunagapally study and the atomic bomb survivor study. In a comparison between the Krunagappally study vs the atomic bomb survivor study + the Techa River (38) study was also made (data not shown in the table). The addition of the Techa River study data did not decrease the P value sizably.

**Table 2.** Comparison of ERR/Gy estimates between the atomic-bomb survivor study and the Karunagappally study

<table>
<thead>
<tr>
<th>Dose (mGy)</th>
<th>Mean dose (mGy)</th>
<th>Cases</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>0.0009</td>
<td>9597</td>
<td>9526.45</td>
</tr>
<tr>
<td>5–</td>
<td>0.0479</td>
<td>4406</td>
<td>4364.63</td>
</tr>
<tr>
<td>100–</td>
<td>0.1489</td>
<td>968</td>
<td>906.61</td>
</tr>
<tr>
<td>200–</td>
<td>0.2985</td>
<td>1144</td>
<td>959.65</td>
</tr>
<tr>
<td>500–</td>
<td>0.7316</td>
<td>688</td>
<td>492.3</td>
</tr>
<tr>
<td>1000–</td>
<td>1.4549</td>
<td>460</td>
<td>247.15</td>
</tr>
<tr>
<td>2000+</td>
<td>2.4933</td>
<td>185</td>
<td>71.34</td>
</tr>
</tbody>
</table>

ERR/Gy estimated from the original RERF data = 0.62 (95% CI: 0.53, 0.70)

ERR/Gy estimated from this table = 0.62 (95% CI: 0.54, 0.70)

In original RERF data, doses are divided into 22 categories. Those dose categories were used when estimating ERRs per dose.

**Summary and Conclusion**

Widely accepted definitions of low and high dose-rates are the dose-rate below 0.1 mGy/min and 0.1 Gy/min or larger, respectively (7). The dose-response relationship between leukemia risk and acute (high dose-rate) exposure to ionizing radiation is linear quadratic (3,4). The estimate of ERR per dose of acute exposure for medium-high dose ranges was a-few-fold larger than that for a low dose range (3,4), and was larger than those obtained from the studies of subjects with exposure to low-medium doses at low-dose rates (9–24). In the case of the solid cancer (or all cancers excluding leukemia), the dose-response relationship is considered to be linear (3,50). Whether the ERR per dose of chronic exposure is lower than that of acute exposure is a topic of debate. The ERR per dose of solid cancer estimated by the study of residents in Karunagappally in Kerala, India (15) was significantly lower than that observed among atomic-bomb survivors as shown in the present study. The meta-analysis of ERR per dose obtained from studies of nuclear workers conducted by Akiba and Mizuno (24) also supported the notion that chronic exposure gives an ERR per dose smaller than acute exposure does. On the other hand, the Techa River study (38,39) gave an ERR per dose similar to what was observed in the atomic-bomb survivor study (3,50). A possible explanation for this finding is that the relatively high-dose-rate exposure may give a higher ERR per dose since the dose rates of radiation exposure in the Techa River cohort were not entirely in the range of low dose-
rates. However, it should also be pointed out that its wide confidence interval does not preclude a possibility that chronic exposure gives an ERR per dose evidently lower than acute exposure does. Our findings are contrary to the dose rate effect of exposure to alpha particles from radon inhalation, in which lower dose-rate exposure to high LET radiation is suspected to be associated with a larger lung cancer risk (51,52).

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References
24 Akiba S, Mizuno S. The third analysis of cancer mortality
41 Degtева MO, Kozheurov VP, Vorobiova MI. General approach to dose reconstruction in the population exposed as a result of the release of radioactive wastes into the Techa River. Sci Total Environ. 1994; 142: 49–61.
47 Ashmore JP, Gentrner NE, Osborne RV. Incomplete data on the Canadian cohort may have affected the results of the study by the International Agency for Research on Cancer on the radiogenic cancer risk among nuclear industry workers in 15 countries. J Radiol Prot. 2010; 30: 121–9.