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Second Analysis of Mortality of Nuclear Industry Workers in Japan, 1986–1997

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A cohort study of nuclear industry workers was initiated in 1990 to determine the possible health effects of low-level radiation. A total of 5,527 deaths were ascertained among 176,000 male workers who had been retrospectively and/or prospectively followed for an average of 7.9 years during the observation period 1986–1997. Statistical analyses were made mainly on the prospective follow-up outcome of 120,000 workers followed for an average of 4.5 years. The standardized mortality ratio (and its 95% confidence interval) was 0.94 (0.90, 0.97) for 2,934 cases of all causes combined and 0.86 (0.82, 0.91) for 1,305 cases of non-malignant diseases combined, which suggested a healthy worker effect. For 1,191 cases of all cancers combined, it was 0.98 (0.93, 1.04), indicating no difference in mortality from that of the general population. In tests for trend of death rate with increasing radiation dose, no significant correlation was found for all cancers combined. For site-specific cancers, most cancers including leukemia showed no positive correlation with dose, except for cancers of the esophagus, stomach and rectum and multiple myeloma. External causes showed a significant correlation with dose. A separate questionnaire study indicated that these positive findings could be ascribed in part to lifestyle characteristics of the workers. For leukemia only, we attempted to estimate the excess relative risk per unit dose of radiation, which, with reservations because of its wide confidence interval, was within the range of variation of the risks reported in other radiation epidemiological studies. This population must be studied for a longer time and with a consideration of the possible effects of confounding factors.

INTRODUCTION

Current radiation protection standards throughout the world are based largely upon the recommendations of the International Commission on Radiological Protection (*1*). The risk estimates adopted in the recommendations rely in part on epidemiological studies of atomic bomb survivors in Hiroshima and Nagasaki who were exposed to high doses of acute radiation (*2*). It was assumed that the findings on cancer mortality from those studies could be extrapolated to low-dose and low-dose-rate radiation exposures with some modifications. However, considerable uncertainties are associated with that extrapolation process, because the biological mechanisms of radiation carcinogenesis are still not well understood (*3*). It is thus important to provide a basis for the adequacy of current radiation protection measures, at least for radiation workers, in terms of the health effects of low-level radiation.

A number of epidemiological studies of nuclear industry workers have been undertaken to obtain information on the health effects of low-dose and low-dose-rate radiation exposure (*4–21*). In Japan, the Institute of Radiation Epidemiology (IRE) of the Radiation Effects Association (REA) initiated a cohort study of nuclear industry workers in 1990. The Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan had entrusted this study to REA. The results of the first analysis, dealing with observations for the period 1986–1992, were reported previously (*17*). The present report presents the results of the second analysis with extension of the observation period to 1997 and with a larger number of study subjects.

MATERIALS AND METHODS

This study was reviewed and approved by the Research Ethics Committee and conformed to the Guidelines for Ethics of Epidemiological Study of the Japanese government.

Population and Follow-up of Vital Status

In Japan, a registry system of radiation workers at nuclear facilities was established in 1977 that is operated by the Radiation Dose Registration Center (RADREC) of REA. Its operational system and database of dose records were described in detail in the previous paper (*17*). The present follow-up study was based upon approximately 244,000 radiation

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workers, including 242,000 males and 2,000 females, who were registered by RADREC as of the end of March 1995 and who satisfied certain requirements such as having a record of exposure dose and Japanese nationality. Compared to our first report (*17*), which dealt with 184,000 workers registered by RADREC as of March 1989, the present study was supplemented by about 60,000 workers, consisting of those who worked only at fuel-processing plants that were excluded from the previous analysis (about 4,000) and those who had first engaged in radiation work after March 1989 (about 56,000).

The requirement of Japanese nationality was set to use residence registration cards (RRC) for follow-up studies. In Japan, every municipality maintains RRC of residents, including their name, date of birth, gender, address, first date of residence, and previous address. If any resident dies or moves to another municipality, the RRC is updated with the date of death or relocation and the next address in the case of relocation and is maintained for exactly 5 years, after which it is deleted from the registration file.

For the follow-up of study subjects, personal identification information was first provided by RADREC, including their central registration number, name, gender and date of birth. Next, their residence address information was obtained with the cooperation of the nuclear facilities at which they worked. Then copies of RRC were acquired from the respective local government offices to ascertain the vital status of the study subjects. Because of the limited period of maintenance of RRC for those who died or emigrated, follow-up checks must be continued at intervals of less than 5 years, since those who have died or emigrated would be lost from the study population otherwise.

Using RRC, the cohort can be followed up both retrospectively and prospectively. For the retrospective observations, the initial date was determined by taking the later of either April 1 of the first year of engagement in radiation work or the date 5 years preceding the date when the RRC was acquired at the first follow-up. Since this follow-up study started in 1991, the earliest year of observation would be 1986. The end of the retrospective observation period was the date when the RRC was first acquired. Among the total population of 244,000 workers, approximately 177,000 (72.6%) were followed up successfully. The remaining workers were lost due to either imprecise address information provided by the respective nuclear facilities or expiration of the storage period of the RRC at the respective municipal offices for deaths or relocations that had occurred prior to the first follow-up.

Prospective follow-up was made for about 120,000 workers who were confirmed to be alive at time of the first follow-up. Thus the initial date of the prospective observation period was the date when the RRC had first been acquired. The terminal date was the date when the RRC had been obtained in the most recent follow-up, the date of death or relocation, or the date of dropout from the study due to failure of follow-up, whenever these events occurred earlier than the closing date of the observation period, i.e. December 31, 1997. Otherwise, this latter date was the terminal date. The dropout rate was only 0.3% of the population, and the majority of this resulted from those who had emigrated from a certain municipality but who for some unknown reason could not be confirmed to have settled successfully in the municipality given as the destination of relocation.

For those whose death was ascertained from the RRC, the cause of death was obtained by record linkage with magnetic tape copies of vital statistics death records (for the period 1986–1997) provided by the Ministry of Health, Labor and Welfare of Japan. Indices used for record linkage were the date of birth, date of death, sex and municipality of residence. Iwasaki *et al.* (*22*) reported successful determination of causes of death by means of this record linkage in 99.7% of subjects.

Radiation Dose Records

The effective dose data registered at RADREC were used to determine the cumulative doses of subject workers. Dosimetry records of radiation workers are prepared by the respective nuclear facilities for the purpose of radiation protection management, and exposure doses are reported to RADREC each year as the annual (mSv), external and internal doses combined. Internal doses were almost negligible. Film badge dosimeters and, especially in recent years, thermoluminescence dosimeters were used for determination of external radiation doses. Doses below the detectable level, which was around 0.1 mSv for γ rays but was slightly variable depending on the different types of dosimeters, were reported to RADREC as *x* values. Such doses were counted as 0 mSv in this study. For dose records missing for such reasons as the loss of dosimeters, the respective facility made estimates of dose based on certain predetermined rules, such as use of measurement by a supplementary dosimeter or use of dosimeters of other workers who had engaged in work at the same time.

Although RADREC initiated the registration in 1978, earlier dosimetry records of workers had been maintained at the respective nuclear facilities back to 1957, and these were provided to RADREC. Consequently, dose data available for this study cover the period from 1957 to 1997; these data were used to calculate the cumulative radiation doses for individual workers. The average annual dose per person has gradually decreased over the years, from about 3.5 mSv before 1982 to about 1.2 mSv after 1990, which is ascribable mainly to technical improvements in procedures to reduce the radiation exposure of workers.

Dose records filed in RADREC reflect changes over time in the definition of radiation quantities and units, advances in the methods of dose measurement and evaluation of dose, and methodological differences between the respective nuclear facilities. The Radiation Dosimetry Committee was organized to investigate and examine from an expert viewpoint the problems involving radiation control practices and the methods of dose measurement and evaluation. The investigations and assessments were carried out based on the results of a questionnaire survey and onsite inspections of all nuclear facilities, and also by taking into consideration various pertinent technical materials. The results of these examinations indicated that the quality of the dose records was adequate and proper for use in this epidemiological study, as described in the previous report (*17*).

Characteristics of the Study Populations

Since the follow-up of the cohort population was made both retrospectively and prospectively, the following two study populations were selected for the statistical analysis. First was the total study population, consisting of approximately 176,000 male workers whose vital status had been verified through either retrospective or prospective follow-up for the period 1986–1997. From this population, approximately 119,000 workers who had been followed up prospectively for the period 1991–1997 were separated and designated as the prospective study population. All of the remaining workers (about 57,000) were those subjects who had been added to the cohort population subsequent to the first analysis. Female workers were excluded from the study populations because they were too few in number, i.e. about 950.

Because follow-up was begun retrospectively by use of RRC in this study, there is no fixed single starting point common for all subjects in the population. Thus Table 1 shows the distribution of the birth years of the study subjects instead of their age distribution at the start of the follow-up. The birth year ranged from 1903 to 1977, thus covering more than 70 years. It appears that the distribution is skewed slightly to later years in the total study population compared to the prospective study population, reflecting the fact that the former population had a larger proportion of those recently engaged in work than the latter.

Table 2 shows the distribution of cumulative doses by the end of 1997 in both the total and prospective study populations. Among those classified in the $<$10-mSv dose class, the dose values for 41% of the total and 38% of the prospective study populations were actually below the detectable level (0 mSv). In 17% of those in the 100+ mSv group, the dose exceeded 200 mSv but was less than 450 mSv. For the total study population, the mean cumulative dose per person was approximately 12.0 mSv and the population dose was about 2,109 person-Sv. The mean cumulative dose per person in the prospective study population was ap-

TABLE 1
Distribution of Birth Years in the Study Populations

Birth years	Total study population Number (%)	Prospective study population Number (%)
1919[a]	1,300 (0.7)	1,055 (0.9)
1920–1929	9,078 (5.2)	7,936 (6.6)
1930–1939	26,105 (14.8)	20,661 (17.3)
1940–1949	42,775 (24.3)	33,171 (27.8)
1950–1959	46,962 (26.7)	35,753 (29.9)
1960–1969	36,745 (20.9)	20,681 (17.3)
1970–[b]	12,974 (7.4)	227 (0.2)
Total	175,939 (100)	119,484 (100)

[a] Four percent of total and 1% of prospective study populations were born earlier than 1910 and the earliest birth year was 1903.

[b] The latest birth year was 1977.

TABLE 2
Distribution of Cumulative Doses to the End of 1997 in the Study Populations.

Cumulative dose groups (mSv)	Total study population Number (%)	Total study population Mean cumulative dose (mSv)	Prospective study population Number (%)	Prospective study population Mean cumulative dose (mSv)
<10[a]	131,809 (74.9)	1.6	83,220 (69.6)	1.7
10–20	16,309 (9.3)	14.3	12,421 (10.4)	14.4
20–50	16,270 (9.2)	31.6	13,197 (11.0)	31.9
50–100	7,390 (4.2)	69.8	6,641 (5.6)	70.2
100+[b]	4,161 (2.4)	154.0	4,005 (3.4)	154.7
Total	175,939 (100)	12.0	119,484 (100)	15.3

[a] Of this class, 41% in the total and 38% in the prospective study populations had 0 mSv exposure.

[b] Of this class, 17% exceeded 200 mSv, but received less than 450 mSv.

proximately 15.3 mSv and the population dose was about 1,826 person-Sv. The difference in mean cumulative dose between the total and prospective study populations reflects the larger proportion of persons in the former group who had recently become engaged in radiation work.

The distributions of calendar year of first engagement in radiation work and length of employment in radiation work in the different dose groups as of the end of 1997 are shown in Tables 3 and 4, respectively, for only the prospective study population. It appears that the higher the cumulative dose, the larger is the percentage who started radiation work in earlier years as well as the percentage who had been working for longer times.

The latest place of residence of study subjects during the observation period was classified into eight major districts from north to south; their distribution in the individual dose groups is shown in Table 5 only for the prospective study population. A large difference in the residence area was observed among the indicated dose groups with statistical significance ($P < 0.0001$ by χ^2 test). Among the eight districts, Kanto was the most common area of residence in lower-dose classes, whereas in the higher-dose classes, residents of Hokkaido and Tohoku, and Hokuriku areas were more common.

The average observation period was 7.9 years per person for the 175,939 workers in the total study population (retrospective and prospective follow-up subjects) and thus generated 1.39 million person-years. In the prospective study population, the average observation period for the 119,484 workers was about 4.5 years per person and thus generated 0.54 million person-years. The mean age at the end of observation period was 45.7 and 49.1 years for the total and prospective study populations, respectively.

Statistical Analysis

Both external and internal comparisons were made using methods similar to those of other radiation epidemiology studies (*4–21*). The total observation period was divided into three calendar-year periods (1986–1989, 1990–1994 and 1995–1997), and the total age range (20 to 84 years) was stratified into 5-year age classes (20–24, 25–29, . . . , 80–84). Observed person-years were calculated separately for each age class by each observation period. Person-years for those over 84 years old were excluded because death certificate diagnosis of causes of death is generally less reliable at older ages. Causes of deaths of interest in this study were primarily all cancers and site-specific cancers, but they also included all causes, non-neoplastic diseases and external causes.

In the external comparison, the standardized mortality ratio (SMR) and its 95% confidence interval (CI) were calculated compared to the general Japanese male population. The SMR is the ratio of observed to expected number of deaths (*23*). The expected number of deaths was calculated by applying the mortality rates of the general Japanese male population in individual age classes and calendar-year periods as described above to the corresponding person-years of the study population.

In the internal comparison, a one-sided trend analysis with z values was performed (*23*). Namely, the study population was divided into five groups by cumulative dose levels, i.e. less than 10, 10–20, 20–50, 50–100 and 100 mSv or more, and the data were tested for whether the ratio of observed (O) to expected (E) number of deaths (O/E ratio) in individual dose groups was increased significantly with increasing cumulative dose. Mean cumulative doses over the respective person-years were used as the scores of individual dose groups. When calculating the expected number of deaths, it was standardized to the mortality of the total population, in addition to the above-mentioned age classes and calendar-year periods. The residence area was also adjusted for by the classification shown in Table 5.

As was seen in the previous section, this population was heterogeneous

TABLE 3
Distribution of Calendar Year of First Engagement in Radiation Work in Different Dose Groups as of the End of 1997 in the Prospective Study Population

Years	Dose group (mSv) <10	10–20	20–50	50–100	100+	Total
–1974	9,763 (11.7)[a]	1,674 (13.5)	2,066 (15.7)	1,309 (19.7)	1,063 (26.5)	15,875 (13.3)
1975–	20,660 (24.8)	3,851 (31.0)	4,225 (32.0)	2,301 (34.6)	1,580 (39.5)	32,617 (27.3)
1980–	29,238 (35.1)	4,553 (36.7)	4,755 (36.0)	2,244 (33.8)	1,132 (28.3)	41,922 (35.1)
1985–	23,559 (28.3)	2,343 (18.9)	2,151 (16.3)	787 (11.9)	230 (5.7)	29,070 (24.3)
Total	83,220 (100.0)	12,421 (100.0)	13,197 (100.0)	6,641 (100.0)	4,005 (100.0)	119,484 (100.0)

[a] Percentage in parentheses.

TABLE 4
Distribution of Duration of Employment in Radiation Work in Different Dose Groups as of the End of 1997

Period (years)	Dose group (mSv)					
	<10	10–20	20–50	50–100	100+	Total
1	28,820 (34.6)[a]	1,843 (14.8)	289 (2.2)	0 (0.0)	0 (0.0)	30,952 (25.9)
2–4	18,367 (22.1)	2,786 (22.4)	2,191 (16.6)	178 (2.7)	1 (0.0)	23,523 (19.7)
5–9	11,507 (13.8)	1,916 (15.4)	2,443 (18.5)	939 (14.1)	160 (4.0)	16,965 (14.2)
10+	24,526 (29.5)	5,876 (47.3)	8,274 (62.7)	5,524 (83.2)	3,844 (96.0)	48,044 (40.2)
Total	83,220 (100.0)	12,421 (100.0)	13,197 (100.0)	6,641 (100.0)	4,005 (100.0)	119,484 (100.0)

[a] Percentage in parentheses.

with respect to various characteristics, such as starting age and starting year of radiation work, duration of engagement in work, residence area and so forth (Tables 3–5), and some of these factors were potential confounding factors in the present study. Among these characteristics, at least residence area would probably be associated with mortality of the study subjects, since a geographic variation in mortality is well known for various kinds of cancer in Japan (*24*). Although it would be better to choose the place of residence in the earlier or main part of life of individuals as a confounder, such information was not available because of the short length of the present follow-up period. We therefore decided to include the latest residence as a potential confounder in the internal comparison. The other factors, though they may also be associated with the mortality of the study subjects, were not adopted as controlling factors simply because the observation period was still too short to adjust for these time-dependent factors in the analysis.

The internal comparison was performed in two ways, either with or without consideration of the latent period for radiation-induced cancer. In dealing with the latent period, we adopted the method used in the study of NRPB in the United Kingdom (*20*). Namely, 2 years for leukemia and 10 years for other cancers were set as the minimum latent periods, and radiation doses were summed from the beginning of radiation work up to these numbers of years before the terminal date of the observation. Thus some subjects might move from a certain dose class to a lower dose class. Similarly, the first 2 years of follow-up for leukemia and 10 years for other cancers, respectively, after first employment to radiation work were excluded from the observation period. Accordingly, the numbers of deaths during these periods were also excluded from the analysis.

If the observed number of deaths was less than 30 and the estimated trend *P* value was lower than 0.10, the results were confirmed by the simulation method (*25*). Furthermore, to avoid inflated detection of statistical significance during repeated multiple tests, supplementary multiple comparison analysis (Bonferroni's method) was performed (*26*).

RESULTS

External Comparison

The total number of deaths was 5,527, including 2,138 cancer deaths, during the observation period 1986 through 1997 in the total study population (Table 6). The SMR (and its 95% CI) for deaths due to all causes, non-neoplastic diseases, and all cancers was 0.90 (0.87–0.92), 0.80 (0.77–0.84) and 0.94 (0.90–0.98), respectively. They were all significantly less than 1. The total number of deaths was 2,934, including 1,191 cancer deaths in the prospective study population during the observation period 1991 through 1997 (Table 7). The SMR (and its 95% CI) for deaths due to all causes, non-neoplastic diseases, and all cancers was 0.94 (0.90–0.97), 0.86 (0.82–0.91), and 0.98 (0.93–1.04), respectively. The former two were both significantly less than 1, whereas that of all cancers was not significantly different from 1. In addition, all of the SMRs for these causes of death were lower in the total study population than in the prospective study population, probably due to a certain amount of incomplete retrospective follow-up (see the Discussion). The SMR for site-specific cancers, including leukemias, was not significantly different from 1 in the prospective study population. Incidentally, no case among the leukemia was certified as chronic lymphocytic leukemia (CLL).

TABLE 5
Distribution of the Final Residence Area of Study Subjects in the Prospective Study Population by the 8 Major Districts in the Entire Country by Dose Group

District[a]	Dose group (mSv)				
	<10	10–20	20–50	50–100	100+
A	11,296 (13.6)[b]	2,296 (18.5)	3,261 (24.7)	2,039 (30.7)	1,585 (39.6)
B	34,481 (41.4)	3,838 (30.9)	3,468 (26.3)	1,504 (22.6)	675 (16.9)
C	6,144 (7.4)	1,309 (10.5)	1,637 (12.4)	890 (13.4)	585 (14.6)
D	6,070 (7.3)	651 (5.2)	788 (6.0)	384 (5.8)	202 (5.0)
E	11,179 (13.4)	1,930 (15.5)	2,029 (15.4)	1,055 (15.9)	603 (15.1)
F	5,431 (6.5)	945 (7.6)	732 (5.5)	256 (3.9)	109 (2.7)
G	2,461 (3.0)	322 (2.6)	278 (2.1)	88 (1.3)	33 (0.8)
H	6,158 (7.4)	1,130 (9.1)	1,004 (7.6)	425 (6.4)	213 (5.3)
Total	83,220 (100.0)	12,421 (100.0)	13,197 (100.0)	6,641 (100.0)	4,005 (100.0)

[a] From north to south, A: Hokkaido and Tohoku, B: Kanto, C: Hokuriku, D: Chubu, E: Kinki, F: Chugoku, G: Sikoku, H: Kyusyu.
[b] Percentage in parentheses.

TABLE 6
SMR by Cause of Death during the Observation Period 1986–1997 in the Total Study Population

Cause of death	Observed number	Expected number	SMR	95% confidence interval	*P* value for two-sided test
All causes	5,527	6,168.8	0.90	(0.87–0.92)	0
External causes	955	902.7	1.06	(0.99–1.13)	0.085
Non-neoplastic disease	2,354	2,933.8	0.80	(0.77–0.84)	0
All neoplasms	2,185	2,332.3	0.94	(0.90–0.98)	0.002
Malignant neoplasms					
All sites	2,138	2,273.9	0.94	(0.90–0.98)	0.005
Oral, pharynx	38	48.3	0.79	(0.56–1.08)	0.159
Esophagus	100	119.3	0.84	(0.68–1.02)	0.085
Stomach	428	481.9	0.89	(0.81–0.98)	0.015
Colon	144	141.6	1.02	(0.86–1.20)	0.875
Rectum	95	109.5	0.87	(0.70–1.06)	0.180
Liver	405	390.2	1.04	(0.94–1.14)	0.471
Gallbladder	70	73.1	0.96	(0.75–1.21)	0.765
Pancreas	127	129.5	0.98	(0.82–1.17)	0.860
Lung	397	410.9	0.97	(0.87–1.07)	0.510
Prostate	32	33.8	0.95	(0.65–1.34)	0.818
Bladder	27	23.4	1.15	(0.76–1.68)	0.525
Kidney and other and unspecified urinary organs	32	37.4	0.86	(0.58–1.21)	0.421
Brain and central nervous system[a]	26	37.7	0.69	(0.45–1.01)	0.067
Non-Hodgkin's lymphoma	46	57.3	0.80	(0.59–1.07)	0.153
Multiple myeloma	20	17.8	1.12	(0.69–1.74)	0.685
Leukemia[b]	60	67.6	0.89	(0.68–1.14)	0.390
All sites except leukemia	2,078	2,206.3	0.94	(0.90–0.98)	0.007

[a] Neoplasm of malignant, benign and unspecified nature.
[b] Number of cases of chronic lymphocytic leukemia was zero.

Internal Comparison

The results of the internal comparison to be presented will be limited to the prospective study population, because, as will be discussed later, retrospective follow-up of the total study population suffered from selection bias. The result of the analysis without consideration of the latent period are shown in Table 8 and those including a correction for the latent period for cancers are presented in Table 9. The total number of deaths with cancer was 1,191 without consideration of the latent period, but it was reduced to 1,076 with inclusion of the latency. The results of analyses were almost comparable between these two groups.

Although the total mortality rate increased significantly with increasing cumulative dose ($P = 0.017$), it was mainly ascribed to deaths due to external causes; the latter showed a clearly and significantly elevated mortality in higher compared to lower dose classes ($P < 0.001$), whereas non-neoplastic diseases showed no apparent trend of increase with dose ($P = 0.371$). For cancers of all sites, though the O/E ratio exhibited a slight tendency of an increase from the lowest to the highest dose classes, the trend was not statistically significant, either with ($P = 0.099$) or without ($P = 0.280$) consideration of the latent period. Even after the exclusion of leukemia, the results remained almost the same. For leukemia, too, no trend of an increase was found ($P = 0.503$ with and $P = 0.538$ without consideration of the latent period).

For site-specific cancers, an increase in the mortality rate with increasing dose was not apparent for most cancers except for cancers of the esophagus ($P < 0.001$ and $P = 0.002$), stomach ($P = 0.025$ and $P = 0.012$) and rectum ($P = 0.024$ and $P = 0.071$), and multiple myeloma ($P = 0.070$ and $P = 0.047$), where the two P values in parentheses are with and without consideration of the latent period, respectively. For multiple myeloma, P values were obtained by the simulation method (*24*). When the multiple comparison test (Bonferroni's method) was applied to the results for these cancers, the trends for cancer of the stomach ($P = 0.382$ and $P = 0.242$) and rectum ($P = 0.370$ and $P = 0.816$) and multiple myeloma ($P = 0.748$ and $P = 0.670$) were found to be non-significant, while a significant trend remained for cancer of the esophagus ($P < 0.001$ and $P = 0.045$).

DISCUSSION

Results of the external comparison revealed that, for major causes of death, the calculated SMR values were generally lower in the total study population than in the prospective one. This may be due in part to the fact that the retrospective follow-up period covered more young and thus newly employed workers than the prospective one, so that the healthy worker effect should be manifested more strongly (*27*). However, it seems probable that the lower

TABLE 7
SMR by Cause of Death during the Observation Period 1991–1997 in the Prospective Study Population

Cause of death	Observed number	Expected number	SMR	95% confidence interval	*P* value for two-sided test
All causes	2,934	3,137.7	0.94	(0.90–0.97)	0
External causes	397	382.7	1.04	(0.94–1.14)	0.481
Non-neoplastic diseases	1,305	1,513.7	0.86	(0.82–0.91)	0
All neoplasms	1,215	1,241.2	0.98	(0.92–1.04)	0.465
Malignant neoplasms					
All sites	1,191	1,212.6	0.98	(0.93–1.04)	0.544
Oral, pharynx	24	26.7	0.90	(0.58–1.34)	0.672
Esophagus	63	65.0	0.97	(0.74–1.24)	0.854
Stomach	230	245.0	0.94	(0.82–1.07)	0.354
Colon	63	77.3	0.81	(0.63–1.04)	0.115
Rectum	49	58.5	0.84	(0.62–1.11)	0.240
Liver	232	206.1	1.13	(0.99–1.28)	0.076
Gallbladder	46	40.1	1.15	(0.84–1.53)	0.391
Pancreas	67	69.9	0.96	(0.74–1.22)	0.779
Lung	238	230.3	1.03	(0.91–1.17)	0.634
Prostate	21	21.6	0.97	(0.60–1.49)	0.985
Bladder	14	13.4	1.04	(0.57–1.75)	0.987
Kidney and other and unspecified urinary organs	20	20.6	0.97	(0.59–1.50)	0.985
Brain and central nervous system[a]	12	17.6	0.68	(0.35–1.19)	0.226
Non-Hodgkin's lymphoma	22	29.5	0.74	(0.47–1.13)	0.195
Multiple myeloma	8	10.1	0.79	(0.34–1.57)	0.622
Leukemia[b]	28	30.9	0.90	(0.60–1.31)	0.661
All sites except leukemia	1,163	1,181.7	0.98	(0.93–1.04)	0.597

[a] Neoplasm of malignant, benign and unspecified nature.
[b] Number of cases of chronic lymphocytic leukemia was zero.

SMR in the total study population was caused mainly by the fact that, at the start of the cohort study, more precise information on residence address could be obtained for workers who were alive and thus currently working compared to those who were deceased. Moreover, since currently employed workers were included more frequently in the higher-dose group than in the lower-dose group, differential follow-up rates were introduced into the retrospective study (data not shown). The prospective follow-up is less affected by this selection bias.

In the prospective study population, external comparisons showed a significantly lower total mortality rate than Japanese males in general, possibly due to the healthy worker effect (*27*). The total cancer mortality rate, for which the influence of this effect is considered to be small (*28–30*), was nearly the same as that of the general Japanese male population. For all site-specific cancers, including leukemia, the mortality rate was not significantly different from that of the general population.

The results of the internal comparisons did not demonstrate any significant trend of an increase in total cancer mortality with radiation dose, either including or excluding leukemia, both with and without consideration of the latent period. No significant trend was found for an increase in leukemia mortality, whereas a significant trend was detected for certain gastrointestinal tract cancers and for multiple myeloma. It should be emphasized that a statistically significant result might be obtained by chance even when low-level radiation may not have a real health effect. Thus multiple comparison analysis was performed for the results of internal comparisons for individual site-specific cancers. With this analysis a significant trend remained only for cancer of the esophagus.

The results of similar studies reported from other countries are quite variable with respect to cancer sites, with a significant association of mortality with radiation dose being found for all sites (*4, 7, 19*), esophagus (*12, 15*), lung (*4, 7, 19*), skin (*14*), bladder (*5*), brain and central nervous system (*15*), multiple myeloma (*5, 6, 14, 16*), leukemia (*5, 8, 10, 13, 14, 16*). Although these results, including those of the present study, are associated with large variations, at least the significant findings for cancer of the esophagus and multiple myeloma, which are in agreement with the present study, deserve attention. For multiple myeloma, however, special emphasis should not be placed on the present results because the observed number of cases was only eight, six of which were in the less than 10 mSv dose class (Table 8). It should be noted that cancer of the pancreas, which showed a positive trend in the first analysis (*17*), demonstrated no increase of mortality in the present analysis.

For cancer of the esophagus, on the other hand, the significant trend with dose observed in the present study is notable because it was confirmed by multiple comparison

TABLE 8
Trend Analysis by Causes of Death during the Observation Period 1991–1997, after Adjustment for Age, Calendar Year and Residence Area, in the Prospective Study Population, without Consideration of the Latent Periods for Cancers[a]

Causes of death	Cumulative dose group (mSv)					χ^2
	<10	10–20	20–50	50–100	100+	*P* value
All causes	2014	320	349	138	113	2.122
	0.97(0.92–1.01)	1.10 (0.98–1.23)	1.13 (1.01–1.25)	0.91 (0.76–1.07)	1.20 (0.99–1.44)	0.017
External causes	236	46	56	31	28	4.372
	0.88 (0.77–1.00)	1.08 (0.79–1.44)	1.21 (0.91–1.57)	1.28 (0.87–1.82)	1.86 (1.23–2.68)	0.000
Non-neoplastic diseases	914	142	150	57	42	0.328
	0.98 (0.91–1.04)	1.11 (0.93–1.31)	1.11 (0.94–1.30)	0.88 (0.66–1.13)	1.04 (0.75–1.41)	0.371
Malignant neoplasms						
All sites	835	125	138	50	43	0.584
	0.98 (0.92–1.05)	1.07 (0.89–1.28)	1.11 (0.93–1.31)	0.82 (0.61–1.08)	1.14 (0.83–1.54)	0.280
Oral, pharynx	18	3	3	0	0	−1.228
	1.05 (0.62–1.66)	1.26 (0.26–3.69)	1.20 (0.25–3.50)	0.00 (0.00–3.02)	0.00 (0.00–4.78)	0.890
Esophagus	38	4	8	10	3	2.891
	0.83 (0.59–1.13)	0.68 (0.18–1.73)	1.32 (0.57–2.60)	3.28 (1.57–6.03)	1.51 (0.31–4.41)	0.002
Stomach	146	32	28	10	14	2.253
	0.90 (0.76–1.05)	1.42 (0.97–2.00)	1.15 (0.76–1.66)	0.82 (0.39–1.51)	1.81 (0.99–3.04)	0.012
Colon	48	4	6	4	1	−0.136
	1.02 (0.75–1.35)	0.72 (0.20–1.85)	1.01 (0.37–2.19)	1.44 (0.39–3.70)	0.61 (0.02–3.42)	0.554
Rectum	32	4	7	2	4	1.469
	0.93 (0.63–1.31)	0.85 (0.23–2.18)	1.34 (0.54–2.77)	0.73 (0.09–2.63)	2.18 (0.60–5.59)	0.071
Liver	164	24	29	8	7	−0.371
	0.99 (0.85–1.16)	1.02 (0.65–1.52)	1.19 (0.80–1.71)	0.68 (0.29–1.34)	0.95 (0.38–1.96)	0.645
Gallbladder	39	2	4	0	1	−1.496
	1.18 (0.84–1.62)	0.47 (0.06–1.69)	0.84 (0.23–2.14)	0.00 (0.00–1.55)	0.62 (0.02–3.47)	0.933
Pancreas	46	11	4	4	2	−0.119
	0.97 (0.71–1.29)	1.63 (0.82–2.92)	0.56 (0.15–1.43)	1.11 (0.30–2.85)	0.95 (0.12–3.44)	0.547
Lung	172	30	26	5	5	−1.397
	1.00 (0.86–1.16)	1.30 (0.88–1.86)	1.06 (0.70–1.56)	0.43 (0.14–1.00)	0.72 (0.24–1.69)	0.919
Prostate	18	0	0	1	2	1.230
	1.14 (0.68–1.80)	0.00 (0.00–2.01)	0.00 (0.00–1.89)	1.07 (0.03–5.94)	3.99 (0.48–14.4)	0.109
Bladder	13	0	1	0	0	−1.437
	1.36 (0.72–2.32)	0.00 (0.00–2.44)	0.58 (0.02–3.22)	0.00 (0.00–4.85)	0.00 (0.00–9.09)	0.925
Kidney and other urinary	12	2	4	2	0	0.116
	0.86 (0.44–1.50)	0.98 (0.12–3.55)	1.82 (0.50–4.65)	1.85 (0.22–6.70)	0.00 (0.00–5.50)	0.454
Brain and CNS[b]	11	0	1	0	0	−1.385
	1.39 (0.69–2.48)	0.00 (0.00–2.69)	0.66 (0.02–3.67)	0.00 (0.00–5.00)	0.00 (0.00–8.22)	0.917
Non-Hodgkin's lymphoma	17	1	3	0	1	−0.239
	1.09 (0.63–1.74)	0.46 (0.01–2.55)	1.30 (0.27–3.80)	0.00 (0.00–3.20)	1.36 (0.03–7.58)	0.595
Multiple myeloma[c]	6	0	0	1	1	—
	1.00 (0.37–2.18)	0.00 (0.00–4.71)	0.00 (0.00–4.59)	3.63 (0.09–20.2)	4.22 (0.18–40.2)	0.047
Leukemia[d]	19	2	5	1	1	−0.095
	0.99 (0.60–1.54)	0.72 (0.09–2.60)	1.57 (0.51–3.66)	0.58 (0.02–3.22)	0.93 (0.02–5.20)	0.538
All site except leukemia	816	123	133	49	42	0.608
	0.98 (0.91–1.05)	1.08 (0.90–1.29)	1.10 (0.92–1.30)	0.83 (0.61–1.10)	1.15 (0.83–1.55)	0.271

[a] Observed number of deaths are shown in the upper row, and O/E ratio (95% confidence interval) are shown in the lower row, respectively. In the rightmost column, trend *z* value and *P* value in the upper row and lower rows, respectively.
[b] Malignant, benign and unspecified neoplasms were included.
[c] *P* value was estimated using the simulation method.
[d] Number of cases of chronic lymphocytic leukemia was zero.

tests. However, examination of the O/E ratio for this cancer, as seen in Table 8 for example, showed the difference to be as large as about threefold between the lowest dose class (<10 mSv) and the two highest dose classes combined (50+ mSv). This magnitude of difference could not be explained as being entirely due to the effect of radiation in view of recent risk estimates obtained from the study of A-bomb survivors (*31*). This difference may have been caused by the influence of confounding factors, such as lifestyle, which were not taken into account in the present study.

One reason to suspect the association of confounding factors with the positive trend observed for certain cancers is the finding for external causes. At present, no explanation can be offered for external causes of death, which showed

TABLE 9
Trend Analysis by Causes of Death during the Observation Period 1991–1997, after Adjustment for Age, Calendar Year and Residence, in the Prospective Study Population for Cancers with Latent Periods of 2 Years for Leukemia and 10 Years for Solid Cancers, Assumed in the Analysis[a]

Causes of death	Cumulative dose group (mSv)					χ^2 *P* value
	<10	10–20	20–50	50–100	100+	
All sites	770	115	124	42	25	1.288
	0.97 (0.90–1.04)	1.09 (0.90–1.31)	1.14 (0.95–1.36)	0.89 (0.64–1.20)	1.27 (0.82–1.88)	0.099
Oral, pharynx	17	2	3	0	0	−0.993
	1.06 (0.61–1.69)	0.92 (0.11–3.33)	1.34 (0.28–3.92)	0.00 (0.00–3.65)	0.00 (0.00–7.82)	0.840
Esophagus	28	6	5	8	3	4.374
	0.75 (0.50–1.08)	1.27 (0.47–2.77)	1.06 (0.34–2.46)	3.77 (1.63–7.42)	3.21 (0.66–9.38)	0.000
Stomach	136	28	26	13	5	1.963
	0.89 (0.75–1.05)	1.36 (0.91–1.97)	1.23 (0.80-1.80)	1.41 (0.75–2.41)	1.30 (0.42–3.04)	0.025
Colon	47	3	7	2	1	−0.018
	1.03 (0.76–1.37)	0.56 (0.11–1.62)	1.26 (0.51–2.60)	0.85 (0.10–3.08)	1.05 (0.03–5.88)	0.507
Rectum	29	3	7	4	2	1.984
	0.88 (0.59–1.27)	0.68 (0.14–1.98)	1.49 (0.60–3.07)	1.88 (0.51–4.81)	2.10 (0.26–7.60)	0.024
Liver	149	21	25	6	6	0.826
	0.98 (0.83–1.15)	1.00 (0.62–1.53)	1.19 (0.77–1.76)	0.67 (0.25–1.46)	1.73 (0.64–3.77)	0.205
Gallbladder	38	3	2	0	1	−1.385
	1.18(0.84–1.62)	0.70 (0.14–2.04)	0.43 (0.05–1.55)	0.00 (0.00–1.89)	1.05 (0.03–5.85)	0.917
Pancreas	44	8	6	1	1	−0.592
	1.00 (0.73–1.34)	1.34 (0.58–2.65)	0.95 (0.35–2.07)	0.37 (0.01–2.04)	0.97 (0.03–5.41)	0.723
Lung	161	25	25	3	3	−1.198
	1.00 (0.85–1.16)	1.21 (0.78–1.79)	1.16 (0.75–1.71)	0.32 (0.07–0.95)	0.75 (0.16–2.20)	0.884
Prostate[b]	18	0	0	2	1	0.741
	1.13 (0.67–1.79)	0.00 (0.00–1.97)	0.00 (0.00–1.91)	2.21 (0.27–7.98)	2.62 (0.07–14.6)	0.229
Bladder	12	0	1	0	0	−1.335
	1.31 (0.68–2.29)	0.00 (0.00–2.73)	0.65 (0.02–3.59)	0.00 (0.00–5.49)	0.00 (0.00–13.0)	0.909
Kidney and other urinary	11	4	4	0	0	−0.254
	0.80 (0.40–1.43)	2.04 (0.56–5.22)	1.99 (0.54-5.10)	0.00 (0.00–4.09)	0.00 (0.00–9.99)	0.600
Brain and CNS[b]	7	1	0	0	0	−1.062
	1.22 (0.49–2.52)	1.09 (0.03–6.09)	0.00 (0.00–4.27)	0.00 (0.00–10.2)	0.00 (0.00–28.9)	0.856
Non-Hodgkin's lymphoma	13	1	3	1	0	−0.058
	0.97 (0.52–1.67)	0.58 (0.02–3.21)	1.68 (0.35–4.91)	1.26 (0.03–7.01)	0.00 (0.00–10.9)	0.523
Multiple myeloma[c]	5	0	0	0	1	—
	1.10 (0.36–2.56)	0.00 (0.00–5.93)	0.00 (0.00–6.71)	0.00 (0.00–18.6)	15.8 (0.40–87.9)	0.070
Leukemia[d]	19	2	5	1	1	−0.009
	0.98 (0.59–1.53)	0.72 (0.09–2.60)	1.58 (0.51–3.68)	0.58 (0.02–3.24)	1.02 (0.03–5.67)	0.503
All site except leukemia	754	112	121	41	24	1.197
	0.97 (0.90–1.04)	1.09 (0.90–1.31)	1.14 (0.95–1.36)	0.89 (0.64–1.21)	1.25 (0.80–1.87)	0.116

[a] Observed number of deaths are shown in the upper row, and O/E ratio (95% confidence interval) are shown in the lower row, respectively. In the rightmost column, trend *z* value and *P* value in the upper row and lower rows, respectively.
[b] Malignant, benign and unspecified neoplasms were included.
[c] *P* value was estimated using the simulation method.
[d] Number of cases for chronic lymphocytic leukemia was zero.

a highly significant trend with radiation dose. External causes consist mainly of suicide and accidents. Almost all previous radiation epidemiology studies (*4–11, 13–18, 20, 21*) have failed to show any increase in these causes of death in relation to radiation exposure, except those of Ashmore *et al.* (*19*), who found a significant positive association of death from accidents with radiation exposure, and those of Gilbert *et al.* (*12*), who found non-significant associations for external causes. They did not interpret these findings.

Since no causal relationship of radiation exposure, especially to such low doses as being considered in this study, could be expected for external causes of death, the present findings were probably influenced by some confounders. Factors associated with these causes of death include the personality, lifestyle, occupation and socioeconomic status of the individuals and the nature of the surrounding society, according to studies in other countries (*32–35*). Although epidemiological studies of these causes of death are limited in Japan, the vital statistics collected by the government (*36*) showed that the mortality rate from external causes of death is characterized by a great variability among different industries.

The possible confounding factors must be taken into consideration since the effect of low-level radiation exposure on cancer mortality is expected to be very small. Since the

present study did not include information on such factors as the lifestyle of the radiation workers, which might be confounding the risk assessment, a questionnaire survey on lifestyle was subsequently performed separately in 1997 through 1999 (*37*). The subjects of that survey were 54,369 males and 470 females currently engaged in radiation work.

A self-administered questionnaire form was distributed to and collected from the subjects by the management of nuclear facilities. Valid answers were obtained from 48,281 male and 428 female subjects. Examination of whether the lifestyle differed among different dose groups was made by the Mantel extension statistical test (*38*) only for the male respondents, with cumulative radiation doses stratified into five classes similarly to those used in this study. The results, in relation to the cumulative radiation dose, could be summarized as follows.

1. A significantly larger percentage of tobacco smokers was found with increasing dose. Furthermore, the number of cigarettes smoked per day was larger and the age of commencement of tobacco smoking was younger in the higher-dose groups.
2. Although the percentage of alcohol drinkers did not differ among the dose groups, those in the higher-dose groups tended to be heavier alcohol drinkers and were younger when they began to drink.
3. Regarding the habit of drinking tea and suchlike, a lower percentage of black tea drinkers was found with increasing cumulative dose.
4. Past history of occupational contact with certain specific harmful materials such as asbestos, organic solvents, etc. was more frequent in the higher-dose groups.
5. Subjects in higher-dose groups underwent X-ray examinations of the upper digestive tract, as well as other kinds of radiological examinations, less frequently.

These results indicated that, among these radiation workers, different dose groups had distinct characteristics in their lifestyles. Though only about 18% (21,700) of the prospective study population examined in the present analysis was also included in that study, the proportion included increased with increasing dose, up to 60% in the 100+ mSv class. Thus it is felt that these results represent the situation among members of the present study population fairly well, and the differences among them in lifestyle may have confounded the results of the present study, particularly with respect to radiation dose.

For instance, tobacco smoking and alcohol drinking are well known to influence the incidence of gastrointestinal tract cancers, especially cancers of the esophagus (*39*). The present finding regarding cancer of the esophagus may be explained in part by this effect. The positive trend of stomach cancer mortality with increasing dose, which cannot be ignored because of the large number of cases detected in the present population, although the trend was not significant by multiple comparison analysis, could also have been brought about by some influence of confounding factors. For stomach cancer, however, tobacco smoking and alcohol drinking are not known to be strongly associated (*40*). Dietary factors such as salt-rich food as well as occupational factors (*41*) should be taken into consideration for this. Furthermore, with respect to the increase in gastrointestinal cancers in higher-dose groups, the last finding (5) in the above-mentioned lifestyle study is especially noteworthy. In Japan, population X-ray examinations of upper gastrointestinal tract cancers have been promoted from the 1970s as a national health policy (*42*). The finding that those in higher-dose classes received examinations less frequently than those in lower-dose classes indicates that the former workers tended to have less recognition of the need for their own health care. Such lifestyle characteristics may increase their mortality rate. At present, however, this is only speculation. The influence of confounding factors in the dose–response relationship between radiation dose and mortality must be examined in more detail.

The excess relative risk of cancer mortality per unit dose of radiation exposure (ERR/Sv) has been estimated in many radiation epidemiology studies (*4, 6–14, 16, 18–21*). This was not done in the present study because the influence of confounding factors was strongly suspected, especially for certain solid cancers. On the other hand, there is no definite evidence of an association of these lifestyle factors with leukemia according to present epidemiological knowledge (*43*). The only factor whose possible confounding influence cannot be totally disregarded is occupational exposure to certain leukemogenic chemical substances, as was suggested from the above-mentioned finding (4) from our questionnaire study (*37*). At present, no data are available on the level of exposure to specific chemical substances among individual radiation workers. Another factor strongly associated with leukemia, especially in Japan, is infection by human T-cell leukemia virus (*44*). However, the main endemic area for this virus is Kyushu island. Only a very small proportion of the present study population resided in this area (Table 5). Thus it seems unlikely that this factor has influenced the present results.

An attempt to estimate the excess relative risk was made only for leukemia mortality by fitting the data to a linear relative risk regression model (*45*) with the AMFIT program (*46*). The ERR/Sv estimates (90% CI) for leukemia obtained in analyses without and with the correction for the latent period were −0.42 (−9.7, 8.9) and 0.01 (−10.0, 10.0), respectively. Because of the wide confidence interval, as was expected from the small numbers of observed cases (Tables 8 and 9), their quantitative evaluation is rather limited. Still, it can be stated at least that the values are within the range (−4.1–7.0) observed in other published studies (*8, 9, 11, 12, 16, 18–20*), some of which (*8, 11, 12, 20*) have estimated ERR only for leukemia other than CLL. Furthermore, compared to the ERR estimate (4.62) from the study of the A-bomb survivors (*31*), the central estimate of the ERR/Sv in our study appears to be very small, even though the difference was not statistically significant.

In conclusion, the present results have not yielded any definite evidence as to whether exposure to occupational low-level radiation increases cancer mortality. The observation period in this study is short, and the average age of the subject population is rather young. Efforts are being made to continue this study over a longer period and to consider the possible effects of confounding factors to obtain more reliable information about the health effects of low-dose and low-dose-rate radiation.

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