Mortality and Cancer Incidence in Misasa, Japan, a Spa Area with Elevated Radon Levels

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A historical cohort study was conducted in Misasa town, Tottori prefecture, Japan, where radon spas have been operating for a long time. Misasa town was divided into an elevated radon level area and a control area, with mean indoor radon levels of about 60 and 20 Bq/m³, respectively. In total, 3,083 subjects in the elevated radon level area and 1,248 in the control area, all aged 40 or older on January 1, 1976, were followed up until December 31, 1993, for a mean period of 14 years. The mortality rates from all causes exhibited no difference between the elevated radon level area and the control area for both sexes. No difference was observed in the incidence of all-site cancers (age, period-adjusted rate ratios by Poisson regression, RR=1.06, 95% confidence interval (CI) 0.79–1.42 for males, RR=0.90, 95%CI 0.65–1.24 for females), while stomach cancer incidence seemed to decrease for both sexes (RR=0.70, 95%CI 0.44–1.11 for male, RR=0.58, 95%CI 0.34–1.00 for female) and lung cancer incidence for males only seemed to increase (RR=1.65, 95%CI 0.83–3.30 for male, RR=1.07, 95%CI 0.28–4.14 for female) in the elevated radon level area. Caution is needed in the interpretation of these findings, however, since the individual exposure level was not measured and major confounding factors, such as smoking and diet, could not be controlled in this study.

Key words: Cancer incidence — Mortality — Radon spa — Indoor radon exposure — Risk

The health effects arising from exposure to low-level radioactive radon-222, one of the important sources of exposure to ionizing radiation in the human environment, remain unclear. Epidemiological studies of underground miners and some experimental studies with laboratory animals have shown that exposure to high-level radon and its decay products may increase the risk of lung cancer.[1–3] Based on the linear no-threshold model, the Environmental Protection Agency (EPA) of the United States recommended that indoor radon levels be kept below 4 pCi/m³ (148 Bq/m³).[4] However, the fact that air in underground mines may contain other lung carcinogens or irritants, and the differences in mode of exposure acquisition make the validity of such an extrapolation uncertain. Also, case-control studies for directly evaluating the effect of residential indoor radon on lung cancer with individual radon measurements have yielded no conclusive results.[5]

Misasa town in Tottori prefecture, with a relatively large population, possesses spas providing hot spring water with a high radon concentration.[6] It is of public concern whether living in the spa area or in other elevated radon level areas poses a hazard to human health. Therefore, following the previous study conducted by Mifune *et al.*,[7] on the basis of recently measured indoor radon concentrations,[8] a historical cohort study for a fixed population was carried out in Misasa town to investigate further the relationship between indoor radon exposure and cancer incidence.

MATERIALS AND METHODS

Study area and measurement of indoor radon concentration Misasa town, with a population of 8,430 in 1995, is located in Tottori prefecture on the mainland of Japan, and is historically divided into five districts—Misasa, Asahi, Takeda, Mitoku and Oshika. Asahi and Takeda are further divided into two districts because of their geographical location (Fig. 1). The spas are located only in Misasa district. From 1992 to 1995, a 24-h measurement of indoor radon concentration in 101 houses in the above seven districts was carried out using the Packard Pico-Rad system.[8] The average (range) of indoor radon concentration (Bq/m³) was 66.2 (25–121) for Misasa, 45.4 (11–78) for Asahi 1 (along the Takase river), 54.1 (15–194) for Asahi 2 (along the Tenjin river), 39.1 (17–90) for Takeda 1 (along the Kadani river), 60.7 (37–109) for Takeda 2
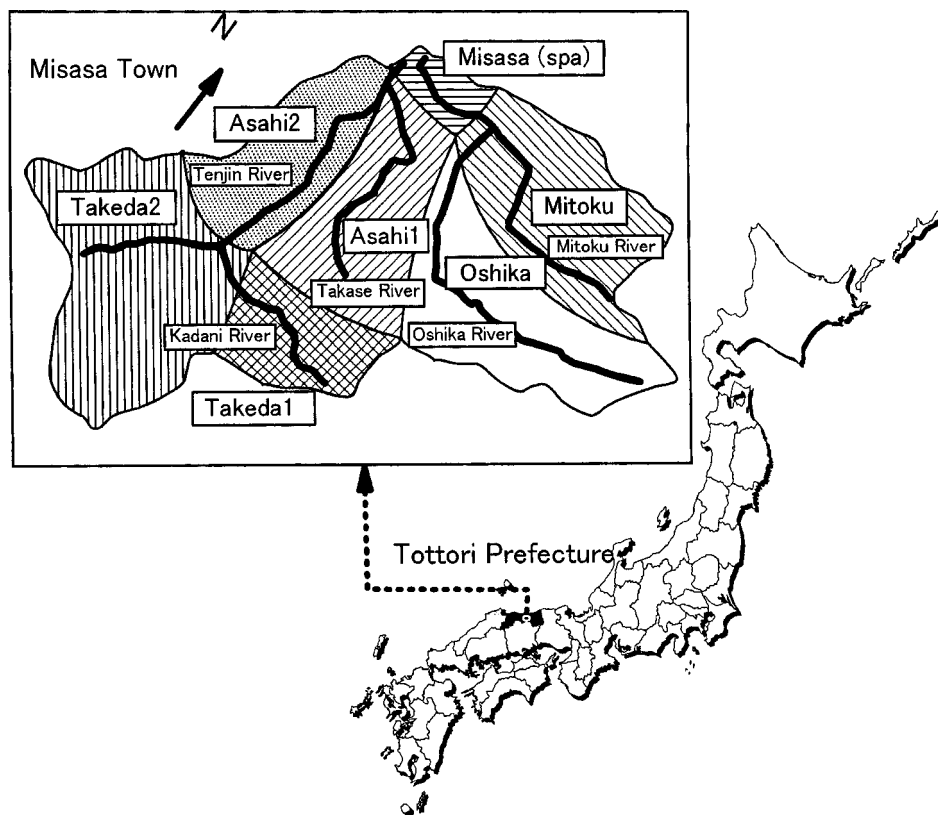
Fig. 1.　Map of Japan with enlargement of Misasa town.

(along the Tenjin river), 25.2 (9–63) for Mitoku and 15.9 (11–22) for Oshika. From the viewpoint of geology, Misasa, Asahi 2 and Takeda 2 belong to the granite zone, while Mitoku, Oshika and Takeda 1 belong to the volcanic rock zone. Asahi 1 has a mixed pattern. Accordingly, the Misasa, Asahi 1, Asahi 2 and Takeda 2 districts were defined as elevated radon level areas, while the Mitoku, Oshika, and Takeda 1 districts were taken as control areas. In the elevated radon level areas, the average (range) of indoor radon concentration (Bq/m^3) was 68.1 (11–194), while in the control areas it was 19.9 (9–90).

Study subjects and data collection The residents in Misasa town, aged 40 or older on January 1, 1976, were selected as study subjects from the Population Registry maintained at the Misasa Town Office. A follow-up was conducted from January 1, 1976 to December 31, 1993. Mortality and migration were confirmed from the Population Registry at the Misasa Town Office. Causes of death were ascertained from death certificates in the Kurayoshi Public Heath Center. The incidence of cancer was traced from the Tottori Cancer Registry.

Statistical procedure For mortality rates, person-years at risk were calculated from January 1, 1976 to December

31, 1993, or to the date of death, whichever came first. For cancer incidence rates, the date of diagnosis of first cancer was used as the end of observation, in addition to the above events for mortality. Second primary cancer was not counted in this analysis. For subjects who emigrated from Misasa town, observations were censored at the date of emigration.

Standardized mortality ratios (SMRs) were calculated using annual sex and age-specific mortality rates in 1976–1993 from the Vital Statistics of Japan as reference rates. Standardized cancer incidence ratios (SIRs) were calculated using the incidence rates observed in Tottori prefecture as reference rates, since nationwide cancer incidence rates covering the entire observation period are not available. Cancer incidence rates in Tottori prefecture were prepared by 10-year age groups and 5-year calendar periods. The significance of SMRs and SIRs was tested assuming the observed number of events followed a Poisson distribution with the mean given by the expected number of events.[9]

In order to compare directly cancer incidence rates in the elevated radon level areas and the control area, Poisson regression analysis was performed by using

GENMOD in the SAS software package.[10] Variables included in the regression model were age (40–59, 60–69, 70–79, 80+), period of study (1976–1985 and 1986–1993) and area (elevated radon level and control areas).

RESULTS

Based on a list in the Misasa Town Office, 4,399 subjects were selected. After exclusion of 68 subjects who migrated between an elevated radon level area and a control area one or more times, 4,331 subjects were defined

as study subjects. The cohort characteristics and SMRs for deaths from all causes and cancer are given in Tables I and II. Mean age at entry was slightly lower in the elevated radon level area than in the control area for both males and females. The percent of emigration was a little higher in the elevated radon level area than that in the control area for both males and females. Throughout the observation, 1,351 deaths were reported, of which 317 were from cancer. For males, the mortality rates from all causes and from cancer in both the elevated radon level area and the control area were not significantly different

Table I. Cohort Characteristics and Standardized Mortality Ratios (SMRs) for Deaths from All Causes and Cancer in Elevated Radon Level and Control Areas, Misasa Cohort, Japan, 1976–1993

	Male		Female	
	ERLA[a]	Control area	ERLA	Control area
No. of study subjects	1,382	564	1,701	684
Mean age at entry (SD)	56.8 (12.3)	57.7 (12.4)	57.8 (12.5)	58.8 (12.6)
Emigration (percent %)	130 (9.4%)	35 (6.2%)	216 (12.7%)	55 (8.0%)
Person-years (mortality)[b]	18,708	7,701	24,235	10,151
Number of deaths from all causes	491	223	435	202
SMR (95%CI[c])	0.93 (0.85–1.01)	0.99 (0.85–1.13)	0.87 (0.79–0.95)	0.86 (0.75–0.99)

a) ERLA, elevated radon level area.
b) Person-years for mortality rate calculation (see text).
c) CI, confidence interval.

Table II. Standardized Mortality Ratios[a] (SMRs) for Deaths from Cancer in Elevated Radon Level and Control Areas, Misasa Cohort, Japan, 1976–1993

Cancer site	ICD-9[b] code	Elevated radon level area				Control area			
		O[c]	E[d]	SMR	95%CI[e]	O[c]	E[d]	SMR	95%CI[e]
Males									
All sites	140–208	140	136.5	1.03	0.86–1.21	58	57.7	1.01	0.76–1.30
Stomach	151	30	39.0	0.77	0.52–1.10	20	16.4	1.22	0.74–1.88
Colon, rectum	153, 154	10	12.5	0.80	0.38–1.47	4	5.3	0.75	0.20–1.93
Liver	155, 156	20	15.8	1.35	0.62–2.56	9	6.7	1.26	0.77–1.95
Lung	162	36	27.1	1.33	0.93–1.84	10	11.5	0.87	0.42–1.60
Leukemia	204–208	5	2.3	2.20	0.71–5.13	2	1.0	2.10	0.24–7.57
Females									
All sites	140–208	80	95.7	0.84	0.66–1.04	39	42.8	0.91	0.65–1.25
Stomach	151	25	23.8	1.05	0.68–1.55	19	10.7	1.77	1.07–2.77
Colon, rectum	153, 154	10	11.6	0.86	0.41–1.58	6	5.2	1.15	0.42–2.50
Liver	155, 156	7	7.5	0.93	0.37–1.91	5	3.4	1.48	0.48–3.46
Lung	162	7	10.1	0.69	0.28–1.43	2	4.5	0.44	0.05–1.59
Leukemia	204–208	4	1.8	2.26	0.61–5.78	1	0.8	1.30	0.02–7.24

a) The respective Japanese nationwide cancer mortality rates were taken as reference values.
b) ICD-9, International Classification of Diseases, Ninth Revision.
c) O, observed number of deaths.
d) E, expected number of deaths.
e) CI, confidence interval.

Table III. Standardized Incidence Ratios[a] (SIRs) for Cancer in Elevated Radon Level Area and Control Area, Misasa Cohort, Japan, 1976–1993, Male

Cancer site	ICD-9[b] code	Elevated radon level area				Control area			
		O[c]	E[d]	SIR	95%CI[e]	O[c]	E[d]	SIR	95%CI[e]
All cancers	140–208, 2331	181	203.0	0.89	0.77–1.03	72	85.6	0.84	0.66–1.06
Oral cavity	141–149	2	3.1	0.64	0.07–2.30	0	1.3	—	—
Esophagus	150	5	5.2	0.95	0.31–2.22	3	2.2	1.36	0.27–3.97
Stomach	151	49	67.8	0.72	0.53–0.96	29	28.5	1.02	0.68–1.46
Colon	153	7	12.0	0.58	0.23–1.20	3	5.1	0.59	0.12–1.72
Rectum	154	5	11.0	0.45	0.15–1.06	3	4.6	0.65	0.13–1.90
Liver	155	22	20.1	1.10	0.69–1.66	8	8.5	0.94	0.41–1.86
Gallbladder, bile ducts	156	1	4.6	0.22	0.00–1.22	3	1.9	1.55	0.31–4.52
Pancreas	157	5	8.7	0.57	0.19–1.34	0	3.7	—	—
Nose, sinuses, etc.	160	2	1.4	1.44	0.16–5.19	0	0.6	—	—
Larynx	161	4	2.8	1.43	0.38–3.66	4	1.2	3.39	0.91–8.68
Bronchus, lung	162	39	31.2	1.25	0.89–1.71	10	13.2	0.76	0.36–1.40
Prostate	185	6	6.7	0.90	0.33–1.95	1	2.9	0.35	0.00–1.94
Bladder	188	6	5.6	1.08	0.39–2.35	1	2.4	0.42	0.01–2.36
Lymphoma	200–203	10	5.1	1.97	0.94–3.63	1	2.1	0.47	0.01–2.59
Leukemia	204–208	5	2.1	2.38	0.77–5.54	2	0.9	2.28	0.26–8.23
Primary site uncertain	159, 165, 195–199	7	5.9	1.19	0.47–2.44	0	2.5	—	—
Other		6	9.5	0.63	0.23–1.38	2	4.0	0.50	0.06–1.81

a) The respective Tottori prefecture population cancer incidence was taken as a reference.
b) ICD-9, International Classification of Diseases, Ninth Revision.
c) O, observed number of deaths.
d) E, expected number of deaths.
e) CI, confidence interval.

from those of the Japanese population as a whole. For females, the mortality rates from all causes and from cancer in both areas were generally low, although only the SMR for death from all causes was statistically significant.

During the follow-up period, 417 incident cases of cancer were ascertained. SIRs for the elevated radon level areas and the control areas are shown in Tables III and IV. Decreased SIRs of all-site cancers were observed for both sexes and in both areas, among which the difference for females in the elevated radon level area was statistically significant (SIR=0.76, 95%CI 0.62–0.91). When classified by site, incidence rates of stomach cancer in the elevated radon level area were lower than those of Tottori prefecture (SIR=0.72, 95%CI 0.53–0.96 for males, SIR=0.73, 95%CI 0.49–1.04 for females, respectively), while those in the control area were similar to or higher than the incidence rates of Tottori prefecture as a whole. Incidence of male lung cancer in the elevated radon level area seemed to be higher (SIR=1.25, 95%CI 0.89–1.71) than that of Tottori prefecture, while it seemed to be lower in the control area (SIR=0.76, 95%CI 0.36–1.40). In females, lung cancer incidence rates in both areas seemed to be lower than that of Tottori prefecture.

When directly compared between the elevated radon level area and the control area, the cancer incidence from all cancers for both males and females showed no difference (Table V). For stomach cancer, decreased relative risks were observed, which were marginally statistically significant. Lung cancer incidence for males in the elevated radon level area was slightly elevated, although it did not reach statistical significance. When the analysis was limited to those born in Misasa town, the results did not change substantially. Although the relative risk for female lung cancer was elevated from 1.07 to 1.85, this result was based on only 4 lung cancer cases after exclusions.

DISCUSSION

The present study on 1976–1993 data affords no evidence that mortality from all causes and cancer incidence at all sites differed between the elevated radon level area and the adjacent control area, as compared to the previous study on 1952–1988 data,[7] which showed statistically significant lower mortality from all cancers in the high radon background area. Reasons for this discrepancy might include the differences in methodology, i.e., a different

Table IV. Standardized Incidence Ratios[a] (SIRs) for Cancer in Elevated Radon Level Area and Control Area, Misasa Cohort, Japan, 1976–1993, Female

Cancer site	ICD-9[b] code	Elevated radon level area				Control area			
		O[c]	E[d]	SIR	95%CI[e]	O[c]	E[d]	SIR	95%CI[e]
All cancers	140–208, 2331	110	145.6	0.76	0.62–0.91	54	63.8	0.85	0.64–1.10
Esophagus	150	1	1.1	0.95	0.01–5.29	1	0.5	2.11	0.03–11.73
Stomach	151	30	41.0	0.73	0.49–1.04	23	18.1	1.27	0.81–1.91
Colon	153	8	10.9	0.73	0.32–1.45	4	4.8	0.83	0.22–2.14
Rectum	154	7	7.3	0.96	0.38–1.97	4	3.2	1.24	0.33–3.19
Liver	155	3	8.3	0.36	0.07–1.05	3	3.7	0.81	0.16–2.38
Gallbladder, bile ducts	156	4	5.9	0.68	0.18–1.74	4	2.6	1.52	0.41–3.89
Pancreas	157	10	6.2	1.62	0.77–2.97	0	2.8	—	—
Nose, sinuses, etc.	160	3	0.9	3.38	0.68–9.87	0	0.4	—	—
Bronchus, lung	162	7	11.3	0.62	0.25–1.28	3	5.0	0.60	0.12–1.74
Breast	174	6	10.9	0.55	0.20–1.20	1	4.5	0.22	0.00–1.23
Uteri	179–182, 2331	8	12.6	0.64	0.27–1.25	2	5.4	0.37	0.04–1.35
Ovary	183	1	3.4	0.29	0.00–1.63	2	1.4	1.20	0.15–4.97
Bladder	188	2	2.1	0.94	0.11–3.39	1	1.0	1.02	0.01–5.66
Lymphoma	200–203	4	3.6	1.10	0.30–2.82	0	1.6	—	—
Leukemia	204–208	4	1.8	2.24	0.60–5.73	1	0.8	1.30	0.02–7.24
Primary site uncertain	159, 165, 195–199	5	5.6	0.90	0.29–2.09	1	2.5	0.40	0.01–2.24
Other		7	11.1	0.63	0.25–1.30	4	4.8	0.83	0.22–2.14

a) The respective Tottori prefecture population cancer incidence was taken as a reference.
b) ICD-9, International Classification of Diseases, Ninth Revision.
c) O, observed number of deaths.
d) E, expected number of deaths.
e) CI, confidence interval.

Table V. Relative Risks of Cancer Incidence for Elevated Radon Level Area versus Control Area by Poisson Regression Analysis for Males and Females, Misasa Cohort, Japan, 1976–1993

Site	All subjects (4,331 persons)				Subjects born in Misasa (2,013 persons)[a]			
	Male		Female		Male		Female	
	Relative risk[b]	95%CI[c]	Relative risk[b]	95%CI[c]	Relative risk[b]	95%CI[c]	Relative risk[b]	95%CI[c]
All sites	1.06	0.79–1.42	0.90	0.65–1.24	0.99	0.72–1.36	0.77	0.44–1.35
Lung cancer	1.65	0.82–3.30	1.07	0.28–4.14	1.67	0.67–4.17	1.85	0.19–17.83
Stomach cancer	0.70	0.44–1.11	0.58	0.34–1.00	0.67	0.40–1.12	0.65	0.24–1.73

a) Only subjects who were born in Misasa and did not move between an elevated radon level and a control area were included in the analysis.
b) Relative risk was calculated by Poisson regression analysis; variables for age, period were also included; incidence in the control area was taken as the reference.
c) CI, confidence interval.

setting of the radon exposure area, sampling problems in the previous study, a different period of survey and a possible undercount of cancer cases in the radon exposure area. The differences of registration rates in the two areas and in the entire Tottori prefecture may also have affected the results. Unfortunately, the Percent of Death Certificate Only (DCO%) in the two areas covering the entire study period could not be calculated. Nevertheless, in 1994, the DCO% for all-site cancers was 21.6% (8/37) and 29.6% (8/27) for the elevated radon level area and the control area, respectively. In 1993, DCO% for all-site cancers in Tohaku county, where Misasa town is located, was

23.5%, which is slightly better than that in all of Tottori prefecture (28.6%). Since there was no great difference in DCO% between the elevated radon level area, the control area and all of Tottori prefecture, the registration rate should have little impact on the results.

In the present study, male lung cancer risk was slightly raised, though the increase was not statistically significant, in the elevated radon level area, whereas no elevated risk was observed in females, which might be due to the few female lung cancer cases. Another explanation might be found in the interaction between radon exposure and smoking, a habit much more prevalent among males than among females in Japan. In fact, animal experiments reveal a multiplicative synergistic relationship[11] and studies with miners suggest a superadditive relationship[1] between smoking and radon exposure. Unfortunately, no smoking data for individual study subjects were available for this study. However, from 1983 the Misasa Town Office organized an annual health check-up program, in which current smoking habits were ascertained by interview. The age-adjusted smoking rates, using the Japanese population in 1985 as a standard population, in the elevated radon level area and the control area were 47.1% and 45.1% for males, and 5.1% and 0.9% for females, respectively. Assuming that the relative risk of lung cancer from smoking in males is 5, the expected risk ratio would be 1.03 for the elevated radon level area, compared to the control area, if other risk factors in the two areas were equal. Therefore, a slightly elevated smoking rate in the elevated radon level area contributes little to the elevated RR observed for male lung cancer. It may be possible that frequent baths in spa springs influence the risk of cancer, since the concentration of radon in the hot spa water is extremely high.[6] However, when the elevated radon level area was further divided into a spa area and other areas without a spa, the relative risks of male lung cancer were 1.23 (95%CI 0.49–3.15) and 1.81 (95%CI 0.93–3.53), compared to the control area. The emigration rate from the elevated radon level area was higher than that from the control area, which might cause bias. Nevertheless, when the analysis was limited to only those born in Misasa town, whose emigration rates were almost the same in the two areas (approximately 3%), the relative risk for male lung cancer remained unchanged, indicating that the difference of emigration should have had no great influence on the results.

In our study, a low incidence of stomach cancer in the elevated radon level area was observed, which is consistent with the results of the previous study,[7] whereas in a combined analysis of 11 studies on miners, an elevated risk of stomach cancer has been reported.[12] However, since no dose-response relation was apparent, those authors proposed that the increased risk of stomach cancer could not be attributed to radon. The risk factors for stomach cancer are mainly diet, other life-style factors, and infection by *Helicobacter pylori*, which could not be controlled in our study.[13] Considering the obviously different population characteristics between our subjects and miners, it is difficult to compare these results directly. Another possible explanation is that radon in drinking water may be a protective factor against stomach cancer. The hypothesis of radiation hormesis, namely the stimulatory action of low-dose irradiation, is a possible mechanism for this.[14] Actually, some of the well water in the elevated radon level area showed a high concentration of radon, up to 400 Bq/liter.[8] However, risk for stomach cancer was lower at a spa area in Beppu, which has only a low radon concentration.[15] Some unknown factors associated with a spa may have protective effects against stomach cancer. However, further investigation is needed to assess the association between radon exposure and stomach cancer.

Several limitations in this study should be noted. First, individual cumulative radon exposure could not be estimated. Radon dosimetry in Misasa town is still inadequate due to the limited number of measurements using only the 24-h Pico-Rad method. Furthermore, the wide range of radon concentration within the districts, especially in the elevated radon level area, indicates that a misclassification of exposure exists. In order to overcome this drawback, we are now conducting a case-control study for lung cancer, measuring the individual indoor radon concentration levels within the same cohort. Second, compared to the indoor radon concentration in other countries, such as Sweden or Finland, the concentration in Misasa town is not very high, even in the elevated radon level area. Given a radon concentration of 70 Bq/m^3 in the elevated radon level area, the cumulative exposure will be 18.5 to 37 working-level-months (WLM) for a 50–100 year duration, and the estimated relative risk for lung cancer will be 1.09–1.18 according to the reported model.[1] The sample size in the present study is not large enough to detect such a low risk. It is reported that the annual nationwide average of indoor radon concentration is 20.8 Bq/m^3.[16] A relatively high average concentration was observed in Hiroshima, Yamaguchi, and Kagawa prefectures. In order to obtain more reliable data, it will be necessary to expand the study areas to include other prefectures.

Conflicting views exist on the relationship between radon exposure and lung cancer. Recently, a pooled analysis on data from 11 studies of radon-exposed miners showed that over the full range of radon exposure, to as low as 50–100 WLM, the relative risk relationship remains linear.[1] Hei *et al.* reported that many cells may survive traversal by one to four particles to express a dose-dependent increase in the frequency of mutations,[17] which may provide a biological basis for the validity of utilizing data from miners, although mutation may not be

directly related to the carcinogenic process. However, the fact that air in underground mines may contain other lung carcinogens or irritants, and the differences in mode of exposure acquisition contribute uncertainties to the linear extrapolation. Due to the difficulty of estimating radon exposure over a lifetime, especially in the dynamic population of Western countries, and incomplete control of confounding factors, the results of the eight case-control studies published to date, in which exposure was estimated by direct measurement of indoor radon concentrations in homes, are viewed as inconsistent and inconclusive.[5] Though a meta-analysis of the above-mentioned eight case-control studies showed a significant exposure-response trend, which is similar to miner-model-based extrapolations, further pooled analysis of more studies is needed.[18] Haynes first reported a negative association between mean radon concentrations in houses and lung cancer standardized mortality ratios in England and Wales.[19] Then a similar study by Cohen also showed an inverse association between the average radon concentration in 1,601 counties of the United States and the respective mortality rates from lung cancer after careful controlling of confounders.[20] But the limitations of an ecological study should be noted in the interpretation of

these results, because of inadequate control of confounding effects due to cigarette smoking.[21]

In general, in spite of the many limitations of this study, the results indicated that living in a radon spa area and in other elevated radon level areas might have no major influence on mortality or all-site cancer incidence. But the effects on cancers of individual sites need to be further investigated by a more extensive study.

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