

Residential Radon Exposure and Lung Cancer Risk in Misasa, Japan: a Case-control Study

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In order to investigate an association between residential radon exposure and risk of lung cancer, a case-control study was conducted in Misasa Town, Tottori Prefecture, Japan. The case series consisted of 28 people who had died of lung cancer in the years 1976–96 and 36 controls chosen randomly from the residents in 1976, matched by sex and year of birth. Individual residential radon concentrations were measured for 1 year with alpha track detectors. The average radon concentration was 46 Bq/m³ for cases and 51 Bq/m³ for controls. Compared to the level of 24 or less Bq/m³, the adjusted odds ratios of lung cancer associated with radon levels of 25–49, 50–99 and 100 or more Bq/m³, were 1.13 (95% confidence interval; 0.29–4.40), 1.23 (0.16–9.39) and 0.25 (0.03–2.33), respectively. None of the estimates showed statistical significance, due to small sample size. When the subjects were limited to only include residents of more than 30 years, the estimates did not change substantially. This study did not find that the risk pattern of lung cancer, possibly associated with residential radon exposure, in Misasa Town differed from patterns observed in other countries.

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INTRODUCTION

Accumulated data indicate that the high levels of radiation exposure can be a cause of lung cancer both in experimental animals¹⁾ and humans²⁾. It has been shown that the radon exposure experienced by uranium miners elevates the risk of lung cancer³⁾. The International Agency for Research on Cancer classified radon gas as a definite human carcinogen⁴⁾. Although the level of exposure is much lower than in mines, a great concern has been raised about the health effects of residential radon exposure, especially for children and females who generally spent long time at home. In order to directly investigate the association between residential radon exposure and lung cancer, several case-control studies have been conducted in North America, Europe and China^{5–12)}. The results to date have been inconsistent and inconclusive. Some studies^{5,7,8,12)} reported positive or weakly positive results, while others^{6,9–11)} reported no increased risk. In a meta-analysis of eight case-control studies conducted in North America, Nordic countries and China, lung cancer risk was to be 1.14-fold for a residential radon level of 150 Bq/m³^{5,13)}. This estimate is consistent with the risk obtained from a pooled analysis of 11 cohorts of uranium miners at a low-dose radon exposure levels^{14,15)}. Although this concordance supports the use of a linear nonthreshold model for risk assessment of residential radon exposure, due caution should be exercised because of the difficulty of estimating radon exposure over a lifetime^{16,17)}.

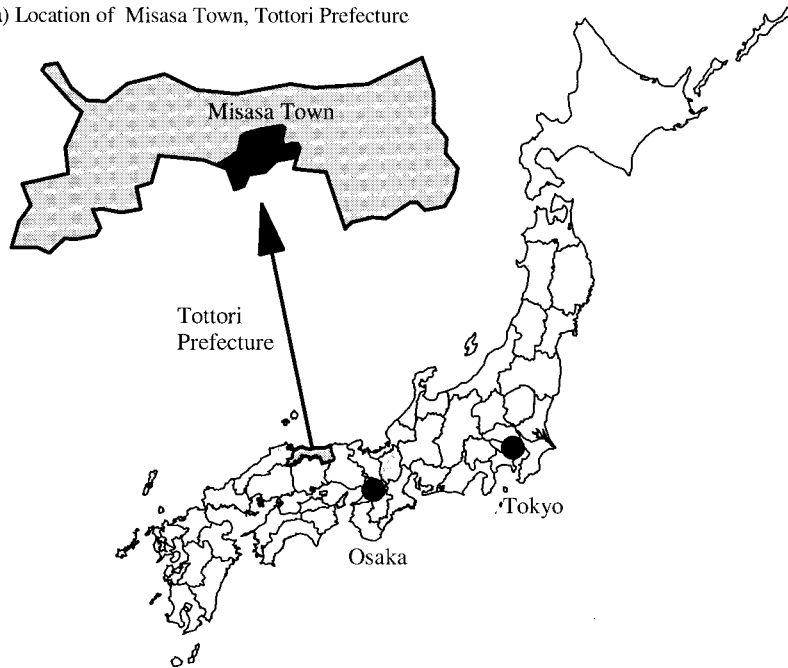
In Japan, it is reported from a nationwide survey of more than 7,000 measurements that residential radon level is about 20 Bq/m³ on average¹⁸⁾. Variation by prefecture across the country shows a tendency for higher levels in south western than in north eastern parts of Japan. The highest average concentration was observed in Hiroshima Prefecture (47 Bq/m³), which was 3.5 times higher than the lowest concentration found in Miyagi Prefecture (13 Bq/m³). In addition, there are some small areas surrounding the radon spas with high residential radon levels. Misasa Town in Tottori Prefecture is one of those radon spa areas, with a relatively large and stable population (Fig. 1). We reported previously that Misasa Town could be divided into elevated radon level areas (Misasa spa, Asahi 1, Asahi 2, Takeda 2) and control areas (Oshika, Mitoku and Takeda 1), with mean residential radon levels of about 60 and 20 Bq/m³, respectively¹⁹⁾. A comparison of cancer incidence between the two areas revealed no difference for cancers of all sites²⁰⁾. A site-specific analysis, however, suggested a decreased risk of stomach and an increased risk of lung cancer in the elevated radon level areas²⁰⁾. In order to further understand the potential effect of residential radon exposure and lung cancer risk, we conducted a case-control study with individual radon measurements in Misasa Town.

MATERIALS AND METHODS

Study subjects

The study population was defined to be all residents of Misasa Town, Tottori Prefecture, Japan, who were 40 years of age or older on January 1, 1976 (n=4,400). From January 1,

(a) Location of Misasa Town, Tottori Prefecture



(b) Distribution of local community in Misasa Town

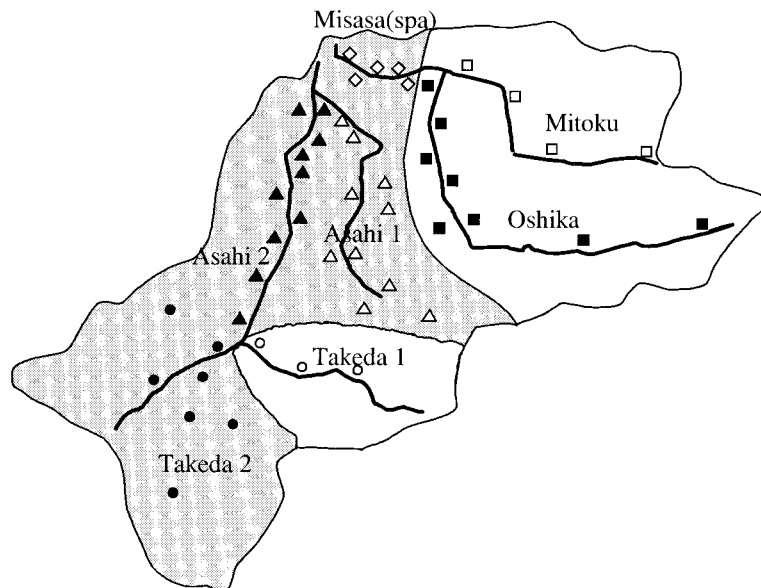


Fig. 1. Location of Misasa Town, Tottori Prefecture, indicated in the map of Japan (a). Distribution of local community in Misasa Town (b). Each symbol represents one local community (...Mitoku, ...Oshika, ... Misasa(spa), ...Asahi 1, ...Asahi 2, ...Takeda 1, ...Takeda 2). Gray and white areas indicate elevated radon level and control areas, respectively, used in the previous study²⁰.

1976 to May 31, 1996, there were 63 lung cancer deaths (54 males and 9 females) according to death certificates. For 51 case subjects (46 males and 5 females), we identified that family members were still living at the address in Misasa Town where the deceased had been living. Permission to measure residential radon was obtained from the family members of 30 cases (28 males and 2 females) either by mail or home visit. A questionnaire on history of smoking, occupation and residence was also completed by the family members, in most cases the spouse (43%), son or daughter (25%) or daughter in law (25%). For each case, 5 control candidates were randomly selected from those in the study population who were alive at the time of death of the corresponding case, matched by sex and year of birth (same year). In the initial round of recruitment, we mailed the consent form for residential radon measurement and the questionnaire to 2 control candidates for each of the 51 potential cases ($n=102$). Of them, 29 control candidates responded by mail agreeing to the measurements. In addition, 9 control candidates agreed to the measurements by home visit. Of these 38 initial control candidates, 13 were adopted as controls for the corresponding matched case, and an additional 5 candidates whose matched cases were not used or already had one control were used as controls for other cases, by allowing the matching criteria for year of birth to expand to within 2 years. For 12 cases which did not have adequate controls, additional recruitment of controls was conducted by home visit, using the list of remaining control candidates. As a result, 36 controls (33 male and 3 female) agreed to residential radon measurements and to fill in the questionnaire. Of them, 16 controls were dead at the time of the survey and questionnaire was completed by family members, usually a son or daughter (50%), daughter-in-law (19%) or spouse (13%).

Measurement of residential radon

Residential radon was measured for 1 year (6 months \times 2) by alpha track detectors (Radtrak, Landauer Inc., Glenwood, Ill USA). It has been shown through comparison with the measurements from electrostatic radon monitors that alpha track detector can accurately measure radon concentration, if the radon concentration is higher than 10 Bq/m^3 and the period of exposure is longer than 6 months²¹). The alpha track detectors were installed during visits to the study subjects' homes. We asked to locate the detector in place where current family members spend the most time, such as living room or bedroom, and 20 cm or more distant from the wall. The detector was collected by home visit at the end of first 6-month measurement period and by mail at the end of second measurement period. The initial measurement began between April and June, 1997 for 51 cases and controls, and for the remaining 15 between July and November, 1997. The second measurement was taken starting between November and December 1997 for 49 cases and controls, for the remaining 15 between February and July, 1998. The weighted average radon concentration of the two measurement periods was calculated by using duration as a weight. For 2 cases, the second measurement was not conducted because family member refused further participation at the end of the first measurement. For 1 case, we failed to collect the detector at the end of the first measurement but 2 detectors were collected at the end of second measurement instead. For this case, the radon measurement from the detector which covered 385 days was used as a weighted average. At

the end, 28 cases (26 males and 2 females) and 36 controls (33 males and 3 controls) were used in further analysis.

Statistical procedure

Residential radon level was divided into 4 categories according to previous studies. The odds ratio of lung cancer deaths associated with residential radon was estimated by either matched or unmatched logistic regression analysis. Since the estimates from both analyses were essentially the same, the results from the latter analysis are presented. Odds ratios were adjusted by year of birth (continuous), sex (male or female), occupational exposure (yes or no) and smoking status (nonsmoker, ex-smoker or current smoker). Actual computation was conducted using PROC LOGISTIC in an SAS program²²⁾.

RESULTS

Table 1 shows the demographic characteristics of cases and controls, as well as those of the study population. The cases who died due to lung cancer were predominantly male and in the older age group. The mean age at the time of death for lung cancer cases was 73.6 years old. Distribution of sex and year of birth was comparable between cases and controls due to matching. Distribution by district showed that controls were oversampled from Misasa spa and undersampled from Asahi 1 and Asahi 2.

Table 1. Demographic characteristics of cases, controls and study population

	Case		Control		Study population	
	N	%	N	%	N	%
Sex						
Male	26	92.9	33	91.7	1,972	44.8
Female	2	7.1	3	8.3	2,428	55.2
Year of birth						
–1896	2	7.1	2	5.6	313	7.1
1897–1906	6	21.4	7	19.4	622	14.1
1907–1916	9	32.1	12	33.3	940	21.4
1917–1926	9	32.1	11	30.6	1,230	28.0
1927–1936	2	7.1	4	11.1	1,295	29.4
District						
Oshika	2	7.1	5	13.9	527	12.0
Mitoku	3	10.7	5	13.9	559	12.7
Misasa spa	6	21.4	19	52.8	1,237	28.1
Asahi 1	3	10.7	1	2.8	548	12.5
Asahi 2	7	25.0	3	8.3	854	19.4
Takeda 1	2	7.1	1	2.8	329	7.5
Takeda 2	5	17.9	2	5.6	346	7.9
Total	28	100.0	36	100.0	4,400	100.0

Table 2. Characteristics of houses used for radon measurements by cases and controls

	Case		Control	
	N	(%)	N	(%)
Years since construction				
Less than 10 years	4	14.3	5	13.9
10–19 years	2	7.1	5	13.9
20–29 years	6	21.4	8	22.2
30–39 years	5	17.9	5	13.9
More than 40 years	9	32.1	11	30.6
Unknown	2	7.1	2	5.6
Type of house				
Wood, single-family house				
one story	9	32.1	5	13.9
two stories	19	67.9	30	83.3
Unknown	0	0.0	1	2.8
History of construction change				
Yes	12	42.9	11	30.6
No	15	53.6	22	61.1
Unknown	1	3.6	3	8.3
Materials of window frame ^a				
Aluminum sash	20	71.4	26	72.2
Wood	4	14.3	7	19.4
Unknown	4	14.3	3	8.3
Air conditioner ^a				
Yes	5	17.9	17	47.2
No	20	71.4	18	50.0
Unknown	3	10.7	1	2.8
Total	28	100.0	36	100.0

^a Room where detector was located

Table 2 shows the construction characteristics of houses selected for radon measurement. Approximately half of the houses were constructed more than 30 years ago. Almost all houses were wood single-family houses of either one or two stories. Remodeling, which were mainly changes of window frames from wood to aluminum sash, was reported for the houses of 42.9% of cases and 30.6% of controls. In the room where the detector was located, the current window frame was aluminum sash in most houses. Air conditioner was more commonly installed in the rooms for controls than for cases.

Table 3 shows the duration and radon concentration of the first and the second measurement period. Mean duration of both measurements was approximately 6 months for both cases and controls. The mean radon concentration of the second measurement tended to be higher than the first measurement period for both cases and controls because the second measurement chiefly covered winter time. Radon concentrations of the first and second measurements were highly correlated with Pearson correlation coefficient of 0.88 ($p < 0.01$).

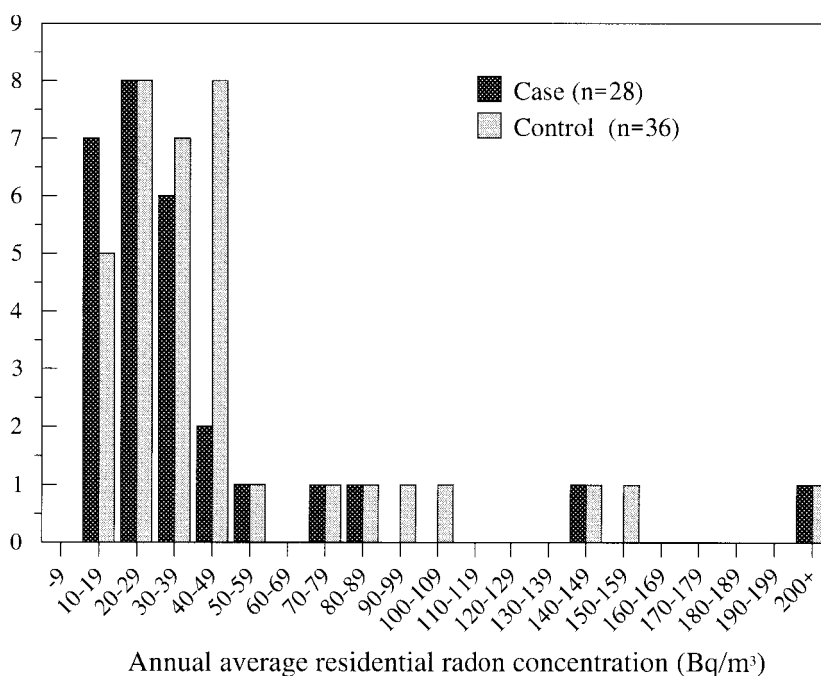
Figure 2 shows the distribution of weighted average radon concentrations among cases

Table 3. Duration and concentration of residential radon measurements for cases and controls

	Case					Control				
	Mean	SD ^a	Med ^b	Min ^c	Max ^d	Mean	SD ^a	Med ^b	Min ^c	Max ^d
First measurement										
Duration (days)	199	41	189	156	385	185	20	180	151	234
Radon concentration (Bq/m ³)	42	47	28	7	222	44	41	31	7	204
Second measurement										
Duration (days)	179	18	183	126	201	181	19	186	134	224
Radon concentration (Bq/m ³)	49	73	31	7	400	58	59	37	11	296

^aStandard deviation^bMedian^cMinimum^dMaximum

Number of residents

**Fig. 2.** Distribution of annual average residential radon concentration for cases and controls.

and controls. Average concentration was slightly higher for controls (51 Bq/m³) than for cases (46 Bq/m³). The maximum concentration was 312 Bq/m³ for cases and 252 Bq/m³ for controls. Two cases (7.1%) and 4 controls (11.1%) had radon concentrations exceeding 100 Bq/m³.

Table 4 shows the distribution of residential history and risk factor status among cases

Table 4. Distribution of residential history and risk factor characteristics among cases and controls

	Male				Female			
	Case		Control		Case		Control	
	N	%	N	%	N	%	N	%
Duration of residence at current address								
From birth (less than 5 years old)	15	57.7	19	57.6	1	50.0	1	33.3
From marriage (20–29 years old)	4	15.4	6	18.2	1	50.0	1	33.3
From more than 30 years old								
Residing over 30 years	4	15.4	5	15.2	0	0.0	0	0.0
Residing less than 29 years	2	7.7	3	9.1	0	0.0	0	0.0
Unknown	1	3.8	0	0.0	0	0.0	1	33.3
Smoking status								
Current smoker	20	76.9	14	42.4	0	0.0	0	0.0
Ex-smoker	3	11.5	10	30.3	0	0.0	0	0.0
Nonsmoker	3	11.5	8	24.2	2	100.0	3	100.0
Unknown	0	0.0	1	3.0	0	0.0	0	0.0
History of occupational exposure								
Yes	3	11.5	1	3.0	0	0.0	0	0.0
No	23	88.5	32	97.0	2	100.0	3	100.0
Total	26	100.0	33	100.0	2	100.0	3	100.0

Table 5. Age and smoking adjusted odds ratio for lung cancer deaths associated with residential radon

Subjects	Case		Control		Adjusted odds ratio ^a (95% confidence interval)
	N	%	N	%	
Residential radon level (Bq/m ³)					
All subjects					
≤24	9	32.1	10	28.6	1.00 ^b
25–49	14	50.0	17	48.6	1.13 (0.29–4.40)
50–99	3	10.7	4	11.4	1.23 (0.16–9.39)
100≤	2	7.1	4	11.4	0.25 (0.03–2.33)
Total	28	100.0	35	100.0	
Residents for more than 30 years					
≤24	8	32.0	8	25.8	1.00 ^b
25–49	13	52.0	15	48.4	1.00 (0.24–4.15)
50–99	2	8.0	4	12.9	0.74 (0.07–7.86)
100≤	2	8.0	4	12.9	0.27 (0.03–2.53)
Total	25	100.0	31	100.0	

^a Adjusted for sex, year of birth, smoking status and occupational history

^b Reference category

and controls. Approximately half of the subjects had lived at the current address, where residential radon levels were measured, since their birth. Only 2 cases and 3 controls had lived at the current address for less than 29 years. Cases showed a higher proportion of current smoker than controls. Among males, 3 cases and 1 control reported an occupational history possibly

associated with the risk of lung cancer, such as mining, stone processing, construction or demolition.

Table 5 shows the odds ratio for lung cancer death associated with residential radon, adjusted by sex, year of birth, smoking status and occupational history. When residential radon level of less than 25 Bq/m³ was used as a reference level, the adjusted odds ratio was estimated to be 1.13, 1.23 and 0.25 for levels of 25–49, 50–99 and 100 or more Bq/m³, respectively. No estimates were statistically significant with a wide confidence interval. When subjects were limited to those who lived at the current address for more than 30 years, no substantial differences were observed.

DISCUSSION

This study is the first case-control study in Japan which evaluated the association of the risk of lung cancer and quantified residential radon exposure. A meta-analysis which summarized 8 case-control studies conducted in North America, Nordic countries and China indicated that the odds ratio of residential radon exposure to the level of 150 Bq/m³ would be 1.14 and that even this magnitude of risk elevation would be important because of the great extent of influence to the general population¹³). Due to limited numbers of cases and controls available, the results in this study are inconclusive in detecting this magnitude of odds ratio. In a previous retrospective cohort study, we reported a potential increase of lung cancer risk (relative risk = 1.65 with 95% confidence interval 0.82–3.30) for males in elevated radon level areas²⁰). However, this increase may be partly due to chance variation or confounded by unadjusted risk factors.

The average residential radon concentration in Japan was reported to be approximately 20 Bq/m³^{5,18}) which is lower than the level reported in North America, Nordic countries and China. In this study, however, the average level was around 50 Bq/m³, which is comparable to the levels indicated in the case-control studies in the above countries. Therefore, if we could expand the study area to include the areas with radon levels similar to Misasa Town, the results may be informative. We measured residential radon levels using the same alpha track detector in 10 houses in the south western part of Tottori Prefecture, which is geologically on old granite rock zone, similar to the high background area in Misasa Town. The average residential radon concentration in this area, however, was around 20 Bq/m³, (maximum 37 Bq/m³) not as high as that in Misasa Town. Therefore, we decided not expand the study to this area.

Besides the small sample size, this study had several other limitations which must be considered. First, the higher proportion of controls was sampled from the Misasa spa district, and the distribution in terms of district was thus not comparable to that of entire study population, which might lead to underestimation of the risk. Actually, among controls, the mean weighted average of residential radon concentration was slightly higher in the Misasa spa district (57 Bq/m³; n = 19) than in Oshika (44 Bq/m³; n = 5), Mitoku (26 Bq/m³; n = 5), Takeda 1 (40 Bq/m³; n = 1) and Takeda 2 (40 Bq/m³; n = 2), but slightly lower than in Asahi 1 (92 Bq/

m³; n = 1) and Asahi 2 (60 Bq/m³; n = 3). Since the controls in Asahi1 and Asahi 2, where radon concentration level was almost the same as in Misasa spa, were under sampled, this sampling bias would not have a substantial influence on the estimates. On the other hand, mean weighted average of radon concentration in Oshika in this study (44 Bq/m³; n = 5) was higher than that observed in the previous measurements (15.9 Bq/m³; n = 9), while that in Mitoku (26 Bq/m³; n = 5) was similar to that observed previously (25.2 Bq/m³; n = 12)¹⁹⁾. Although this may be due to chance variation because of small numbers, 2 residents which showed rather high radon levels in Oshika (70.8 Bq/m³ and 85.7 Bq/m³) were located at 2 local communities in the east part of Oshika and geologically this area belongs to old granite rock zone. Therefore, it may be better to classify this area in Oshika into elevated radon level area, but the influence of this change will be minimal because of very few population in this area.

Second, residential radon concentration measured for one year was used as a surrogate for cumulative radon exposure. Although this may not be valid, there is no alternative practical approach. In this study, over half of the study subjects were living at the address where residential radon concentration was measured, in houses which had been constructed more than 30 years before. Therefore, the current measurements may well reflect the lifetime cumulative exposure. However, 30 to 40% of the houses had undergone changes, mainly in window frame materials, from wood to aluminum sash. Since air tightness tends to increase with aluminum sashes installation, radon concentration could be higher when using the current measurements.

Third, since the case series were obtained from death certificates, all cases were deceased and information on confounding exposures, such as smoking, had to be collected from family members. In the case of lung cancer, although the use of incidence data would not have great difference from the using mortality data because of the low survival rate, it would be preferable in a study on etiology. However, at present the use of population-based incidence data with individual identification from a population-based cancer registry is not allowed for analytical study, as population-based cancer registries prohibit investigators from contacting registered patients personally. Discussion is needed for the appropriate use of individual cancer incidence data from cancer registries in analytic research, when additional contact to registered patients is necessary. At least in this study, however, the information we collected for confounding, such as history of smoking, occupation and residence, was generally reliable as it was collected from close family members²³⁾.

Fourth, in order to accumulate as many lung cancer cases as possible, we extended study period to over 20 years. This resulted in the fact that a substantial number of cases (12 out of 63) could not be surveyed because no family member remained. In addition, response from family members on confounders would be less accurate for the case subjects who died many years ago. A shorter study period covering a large population would be a preferable design for this type of investigation.

Currently, 11 additional case-control studies are being conducted in several countries, preparing for a future meta-analysis with about 12,000 lung cancer cases^{16,17)}. Unfortunately, the present study could not make a contribution to these collaborative efforts. At least, however, this study indicates that there is no reason that the risk of lung cancer due to residential

radon estimated from the above the meta-analysis cannot be applied in Japan. There is a possibility of conducting a large-scale case-control study in Japan, but since residential radon levels are not high, the study efficiency should be carefully examined before implementation.

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