Increased Risk of Lung Cancer Mortality among Residents near an Asbestos Product Manufacturing Plant

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We investigated whether individuals exposed to asbestos by living near an asbestos-manufacturing facility experienced increased lung cancer mortality. We studied a neighborhood around such a plant in the central Japanese city of Hashima. From 1943 to 1991 this plant produced insulation and packing material using amosite- and chrysotile-type asbestos fibers. The study group was comprised of 577 households. We obtained demographic information by a questionnaire and determined the underlying cause of death for deceased household members from death certificates. Using hourly meteorological data from local observatories, we estimated relative asbestos concentrations in the plant's vicinity, determined the quartile boundaries, and designated each study subject's quartile of ambient exposure. Finally, we calculated standardized mortality ratios to evaluate the association of residential asbestos with lung cancer risk. Our findings strongly suggest that neighborhood asbestos exposure can increase the risk of lung cancer mortality in men and probably in women. *Key words*: asbestos; neighborhood exposures; lung cancer; mortality; Hashima, Japan.

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INTRODUCTION

Many cohort studies of asbestos workers have demonstrated that occupational asbestos exposure causes both lung cancer and malignant mesothelioma.[1-9] Focusing on neighborhood asbestos exposure, several epidemiological studies have shown that people who resided near asbestos mines and asbestos product plants have increased risk of developing mesothelioma.[10–19] This study addresses a different question regarding asbestos contact: whether neighborhood asbestos exposure leads to excess lung cancer mortality. While some studies[16,20–23] have examined lung cancer deaths in people who have lived in the vicinity of asbestos plants, only one investigation[22] conducted mortality analysis after excluding lung cancer cases with occupational and domestic asbestos exposure. It did not find statistically significant excess risk of lung cancer death.

From 1943 to 1959, Sogakuseisakusyo Corporation operated an asbestos product plant in the city of Hashima, located in the central Japanese prefecture, Gifu. Ownership changed to Nichias Corporation in 1960, which ran the plant until 1991. The first company produced insulation material and packing material, but little is known about the type of asbestos used. Under the subsequent owners, the facility manufactured insulation, calcium silicate board, and packing material using predominantly amosite and chrysotile fibers plus a small amount of crocidolite. Annual amounts of amosite and chrysotile produced were estimated to be several thousand metric tons. By March 2009, a minimum of 25 former employees in the plant had developed lung cancer and at least 17 former workers had been diagnosed with mesothelioma.[24]

In 2007, Hashima's municipal government performed medical examinations on 298 residents who had lived in the city before 1977. These exams revealed that of 161 residents who did not have occupational or domestic asbestos exposure, 41 (26%) had pleural plaques visible on chest films.[25] According to a 2006 newspaper article, a woman who died from pleural mesothelioma in 1989 had resided near the plant but had never worked with asbestos.[26] Another article, published in 2007, reported that a women who had worked at a hospital adjacent to the plant also contracted the disease.[27] These findings suggested that the plant's asbestos emissions posed substantial health risks for area residents. The aim of this study was to investigate the relationship between estimated concentrations of ambient neighborhood asbestos and lung cancer mortality among vicinity residents. Our study was approved by the Ethics Committee of the Osaka Prefectural Institute of Public Health.

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METHODS

Cohort Definition

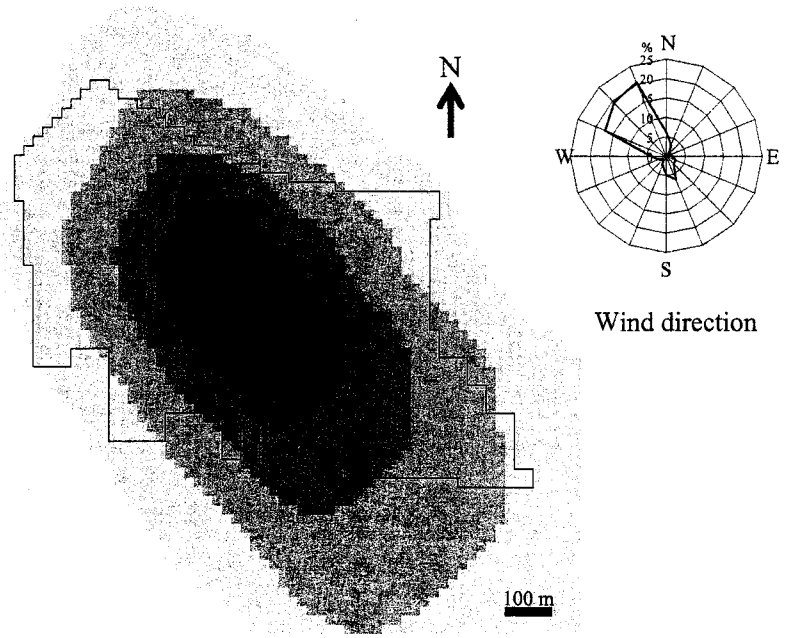
The city of Hashima is subdivided into districts ("chou" or "choume" in Japanese); each district is comprised of 50 to 150 houses and represented by a community association. We invited the community associations of 11 districts near the asbestos plant to participate our study, and eight of the associations agreed. This collective area became the study area and is circumscribed by the black line in Figure 1. The districts of the remaining three community associations that did not participate to our study are on the north side of the study area.

Based on a city map showing houses and family names, we identified 739 households that were living in the study area as of January 1992. We defined "household" as a group of family members who lived together in a house and "household member" as an individual person of the family. These individuals had lived in this area since some point before 1991, so they had to be exposed to asbestos emitted from the plant. Based on information from the community associations, we identified 577 households in which at least one person lived until June 30, 2007, the conclusion of our study. All members of these 577 households, regardless of whether they were living or deceased, or no longer living in the area, were designated study subjects. In the remaining 162 households, all members had either moved out of the area or died by June 30, 2007. We excluded them as subjects because of difficulties in data collection.

Data Collection

We asked the community associations to deliver questionnaires to the representative head-of-household for each of the 577 homes. The questionnaire asked for the number of household members who resided in the home as of January 1, 1992 and numbers of deceased persons and survivors as of June 30, 2007. Furthermore, we collected demographic information, including name, sex, date of birth, first year residing in the area, smoking history, and vitality status (living or deceased) as of June 30, 2007 for all members; we obtained date of death for deceased persons. Smoking history was ascertained through questions on smoking status (current smoker, ex-smoker, or non-smoker for survivors; smoker or non-smoker for deceased persons), smoking amount (cigarettes/day), and smoking duration (ages started and stopped smoking). In the event that we received incomplete information, we repeatedly queried the respective household representative by mail, telephone, and/or personal visit.

In the case of deceased household members, we obtained residence certificates from the Hashima municipal office and verified the demographic information questionnaire data (name, sex, date of birth, date of death, and first year of residence in the area). We also collected death certificates from the district's



: 22.4 to 43.5 m^{-3} (exposure group 1), : 43.5 to 91.8 m^{-3} (exposure group 2),
: 91.8 to 211.2 m^{-3} (exposure group 3), : 211.2 to 1586.8 m^{-3} (exposure group 4)

Figure 1—Wind direction and estimated relative asbestos concentrations. (Asbestos plant designated by black shape; study area is within black line)

Legal Affairs Bureau and noted the cause of death (COD). If COD was asbestos-related disease such as asbestosis, mesothelioma, or lung cancer, we asked the head-of-household to provide an entire lifetime chronological table showing deceased individuals' occupational and residential histories, as well as all household members' occupations. If there was a gap in the chronological table, we repeated our request for the head-of-household to complete the histories. On the basis of both job descriptions provided by the head-of-household and a list of job categories with potential asbestos exposure,[28] one of our authors (SK), an industrial hygienist, assessed the possibility of job-related exposure. When the information provided by household members was insufficient, we interviewed deceased persons' coworkers. Jobs were first classified as: (1) definite asbestos exposure, (2) possible asbestos exposure, or (3) non-exposure. Finally, we combined the definite and possible categories into "occupational asbestos exposure."

Estimation of Relative Asbestos Exposure Concentration

Because it was not possible to ascertain actual airborne asbestos concentrations retrospectively (that is, at the time of the study subjects' exposures), we estimated "relative asbestos concentrations" (unit: m^{-3}) using a procedure described in our earlier study of neighborhood asbestos exposure.[19] Specifically, we obtained hourly measurements of wind velocity, wind direction, and relative sunshine duration from the nearest meteorological observatories. Since hourly monitoring information was not available before 2002, we used data from the years 2002 to 2006—confirming that local meteorological and geographical conditions were consistent from 1975 to 2006.[29] The observatory that monitored wind velocity and direction was located one kilometer (km) south-southwest and the other that tracked relative sunshine duration was situated nine km northeast of the plant. The facilities provided 43,824 hours of meteorological data, representing 99.7% of the hours in the five-year period. We classified the 43,824 meteorological conditions into 1536 patterns based on two wind attributes (velocity and direction) in conjunction with air stability class. The stability class was determined from the wind velocity and relative sunshine duration using a modified Pasquill's method.[30] We then calculated the relative frequency of each of the patterns.

A square area of 1.6 km from east to west and 1.6 km north to south, centered at the Nichias asbestos plant was subdivided into 6400 grids of 20 m × 20 m (Figure 1). Our study area was included within the square area of 1.6 km. The estimation was based on three assumptions:

1. The Nichias plant was the only source of industrial asbestos emissions in the vicinity. There were no other large asbestos manufacturers within Hashima city.
2. The designated point source of asbestos emissions was the center of the plant at zero meters height.
3. Because the emission rate of asbestos between 1943 and 1991 was unknown, we simplified our calculations using the amount of 10^7 per second.

The asbestos concentration at the center of each of the 6400 grids was calculated by a diffusion equation[31] for each of the 1536 meteorological patterns. The asbestos concentration was multiplied by the relative frequency of the meteorological pattern, and finally these 1536 products were summed to yield the relative asbestos concentration over the entire period.

By locating a study subject's house within a particular grid, his or her asbestos exposure was assumed to be the estimated concentration within that grid. Finally, the subjects were categorized according to exposure quartiles (exposure groups 1 to 4) in ascending order of asbestos exposure concentrations.

Data Analyses

Because asbestos was used in the plant from 1943 to 1991, we assumed that the first year of exposure was 1943 among subjects whose residence in the study area predated this time period; for remaining subjects we considered their first exposure to be their first year living in the study area. The last year of asbestos exposure was assumed to be 1991 for all subjects. To quantify smoking exposure, we determined each subject's Brinkman index as of 1992 (smoking amount multiplied by smoking duration).

We used χ^2-tests to evaluate differences in relative frequency distributions of birth year, first exposure year, age at first exposure, and smoking status among the four exposure groups. Subsequently we used analysis of variance (ANOVA) to evaluate differences in the Brinkman index. To compare individuals who died from lung cancer and those who died from other causes, we used the χ^2-test to analyze differences in birth year, first year of asbestos exposure, age at first asbestos exposure, asbestos exposure intensity, and smoking status, and we used the *t*-test to analyze differences in the Brinkman index.

Guided by the International Classification of Disease, Revision 10 (ICD 10) rules, we selected an underlying cause of death from diseases described in the death certificate for each of the deceased persons. Subsequently we computed the person-year experiences of each subject beginning with January 1, 1992 until either the date of their death or the end of the follow-up period (June 30, 2007), and calculated "expected deaths" using sex, age, calendar year, and cause-specific death rates among the Japanese population. Then, we computed standardized mortality ratios (SMRs)—the

ratio of observed deaths to expected deaths. Finally, we calculated 95% confidence intervals (95%CIs) around each SMR by treating the observed number of deaths as a Poisson distribution variable.

RESULTS

Characteristics of Cohort

We were able to obtain complete follow-up information, except for smoking amount and duration, for 502 of the 577 households (87.0%). For smoking amount and duration, we obtained the information for only 63.0% of current or ex-smokers, and attributed this percentage to recall difficulty on the part of the respondents.

Table 1 shows demographic characteristics for members of the 502 households. There were 951 men and 956 women. We observed 13,935 person-years in men and 14,128 person-years in women. One hundred fifteen men and 113 women had died by June 30, 2007. Five hundred fifty-one (58%) men and 611 (64%) women were born before 1960. Regarding their ambient asbestos exposure, 583 (61%) men and 554 (58%) women were first exposed prior to 1975, and 764 (80%) men and 766 (80%) women were first exposed before age 30. Examining smoking history, a known cause of lung cancer and therefore a potential confounding factor, 308 (37%) of male survivors and 73 (5%) of female survivors were current smokers. Of surviving subjects aged 20 and older, 39% of men and 5% of women were current smokers. According to household representatives, 73 (62%) of deceased men and 14 (12%) of deceased women had smoked. Brinkman indices in men and women with smoking history were 480 and 340 cigarettes/day, respectively, as of January 1992.

Mortality among the Whole Cohort

Table 2 presents the numbers of cause-specific observed and expected deaths, and their corresponding SMRs with 95% CIs. Neither men nor women experienced significantly higher overall mortality. But the analyses did show statistically significant increased risk of death for lung and central nervous system malignancies in men and for "external causes" (ICD 10) in women. None of the study subjects died from malignant mesothelioma.

Occupational Asbestos Exposure in Lung Cancer Deceased Persons

Of the subjects who died from lung cancer (22 men and five women), seven men and one woman had occupational asbestos exposure. Of these individuals, three men and one woman worked in the asbestos plant (definite exposure), three men worked in construction (possible exposure), and one man was a car mechanic (possible exposure). The remaining 15 men and four women were not occupationally exposed to asbestos, nor did they live with an asbestos worker. The mortality from lung cancer did not significantly increase for either men or women (Table 2). Two of the 15 men who did not have occupational asbestos exposure did, however, work in a foundry for several years. In this job they may have had contact with silica, an established lung carcinogen.[32]

Lung Cancer Mortality in Each Exposure Group

In the 1.6 km × 1.6 km square area, we estimated that the relative asbestos concentrations in each 20 m × 20 m grid ranged from 3.1 to 2353.5m^{-3}. We calculated the subjects' individual asbestos exposures to be a minimum of 22.4 to a maximum of 1586.8 m^{-3}. When partitioned into quartiles, the corresponding personal exposures were: exposure group 1: 22.4 to 43.5 m^{-3}; exposure group 2: 43.5 to 91.8 m^{-3}; exposure group 3: 91.8 to 211.2 m^{-3}; and exposure group 4: 211.2 to 1586.8 m^{-3}.

Figure 1 illustrates these four exposure areas. Grids with the highest relative asbestos concentrations were found disproportionately to the southeast of the plant—a logical phenomenon given that the area's predominant wind pattern originated from the northwest and blew in this direction.

In exposure groups 1 to 4, our follow-up rates for households were 89.9%, 83.6%, 84.2%, and 91.0%, respectively. Demographic characteristics by gender and asbestos exposure group are presented in Table 1. There were no significant differences in birth year, age at first asbestos exposure, and smoking history among the four levels of asbestos exposure for both genders. By contrast, the dates of first asbestos exposure was significantly different among the four groups for both genders. The cumulative exposure (the product of relative asbestos exposure concentration and exposure duration) increased successively with more highly exposed groups.

Table 3 presents male and female SMRs for all causes of death and for lung cancer in each of the four exposure groups. Although all-cause mortality did not increase significantly for any gender–exposure subgroup, lung cancer deaths increased significantly for both genders in exposure group 4. When the eight lung cancer cases with occupational asbestos exposure were excluded from the analysis, the numbers of lung cancer deaths in exposure groups 1 to 4 were two, one, four, and eight, respectively, in men; and zero, one, zero, and three, respectively, in women. The increased risk for males in exposure group 4 remained significant, but the finding regarding females did not. This phenomenon persisted, even after eliminating two men with occupational silica exposure from the analysis.

Table 3 also lists the SMRs for circulatory and respiratory diseases to show the impact of exposure level on other causes of death. The data revealed that the only

TABLE 1 Demographic Characteristics of Study Subjects

	Men						Women					
		Exposure Group[a]						Exposure Group				
	All	1	2	3	4	p-value	All	1	2	3	4	p-value
Number	951	225	249	243	234		956	253	229	232	242	
Follow-up (person-years)	13,935	3270	3661	3565	3439		14,128	3739	3409	3430	3549	
Relative asbestos exposure concentration (m^{-3})												
Mean		33	63	136	480			33	63	139	458	
SD		6	14	32	307			6	14	33	285	
Cumulated exposure (m^{-3} yr)[b]												
Mean		800	1290	3460	10,400			690	1310	3300	9950	
SD		460	890	2350	9700			440	870	2070	10,400	
Status at follow-up (n (%))												
Living	834 (87.7)	196 (87.1)	222 (89.2)	212 (87.2)	204 (87.2)	0.881	843 (88.2)	229 (90.5)	203 (88.6)	200 (86.2)	211 (87.2)	0.482
Deceased	117 (12.3)	29 (12.9)	27 (10.8)	31 (12.8)	30 (12.8)		113 (11.8)	24 (9.5)	26 (11.4)	32 (13.8)	31 (12.8)	
Year of birth (n (%))												
1905–1944	360 (37.9)	82 (36.4)	89 (35.7)	100 (41.2)	89 (38.0)	0.936	395 (41.3)	97 (38.3)	95 (41.5)	106 (45.7)	97 (40.1)	0.650
1945–1959	191 (20.1)	49 (21.8)	47 (18.9)	47 (19.3)	48 (20.5)		216 (22.6)	56 (22.1)	56 (24.5)	47 (20.3)	57 (23.6)	
1960–1974	205 (21.6)	52 (23.1)	56 (22.5)	48 (19.8)	49 (20.9)		177 (18.5)	45 (17.8)	41 (17.9)	45 (19.4)	46 (19.0)	
1975–1991	195 (20.5)	42 (18.7)	57 (22.9)	48 (19.8)	48 (20.5)		168 (17.6)	55 (21.7)	37 (16.2)	34 (14.7)	42 (17.4)	
Year of first exposure (n (%))												
1943–1944	102 (10.7)	31 (13.8)	20 (8.0)	33 (13.6)	18 (7.7)	0.006	64 (6.7)	23 (9.1)	17 (7.4)	13 (5.6)	11 (4.5)	0.023
1945–1959	159 (16.7)	38 (16.9)	29 (11.6)	46 (18.9)	46 (19.7)		154 (16.1)	32 (12.6)	28 (12.2)	46 (19.8)	48 (19.8)	
1960–1974	322 (33.9)	80 (35.6)	79 (31.7)	82 (33.7)	81 (34.6)		336 (35.1)	84 (33.2)	81 (35.4)	93 (40.1)	78 (32.2)	
1975–1991	368 (38.7)	76 (33.8)	121 (48.6)	82 (33.7)	89 (38.0)		402 (42.1)	114 (45.1)	103 (45.0)	80 (34.5)	105 (43.4)	
Age at first exposure (n (%))												
0–14	534 (56.2)	140 (62.2)	132 (53.0)	139 (57.2)	123 (52.6)	0.452	352 (36.8)	98 (38.7)	84 (36.7)	79 (34.1)	91 (37.6)	0.477
15–29	230 (24.2)	45 (20.0)	66 (26.5)	61 (25.1)	58 (24.8)		414 (43.3)	118 (46.6)	93 (40.6)	103 (44.4)	100 (41.3)	
30–44	147 (15.5)	34 (15.1)	41 (16.5)	31 (12.8)	41 (17.5)		136 (14.2)	28 (11.1)	36 (15.7)	38 (16.4)	34 (14.0)	
≥45	40 (4.2)	6 (2.7)	10 (4.0)	12 (4.9)	12 (5.1)		54 (5.6)	9 (3.6)	16 (7.0)	12 (5.2)	17 (7.0)	
Smoking history												
Surviving subjects (n (%))												
Current smoker	308 (36.9)	75 (38.3)	84 (37.8)	65 (30.7)	84 (41.2)	0.284	41 (4.9)	16 (7.0)	5 (2.5)	8 (4.0)	12 (5.7)	0.234
Ex-smoker	222 (26.6)	57 (29.1)	54 (24.3)	59 (27.8)	52 (25.5)		23 (2.7)	9 (3.9)	5 (2.5)	3 (1.5)	6 (2.8)	
Non-smoker	304 (36.5)	64 (32.7)	84 (37.8)	88 (41.5)	68 (33.3)		779 (92.4)	204 (89.1)	193 (95.1)	189 (94.5)	193 (91.5)	
Deceased subjects (n (%))												
Smoking history	73 (62.4)	17 (58.6)	17 (63.0)	20 (64.5)	19 (63.3)	0.969	14 (12.4)	2 (8.3)	6 (23.1)	3 (9.4)	3 (9.7)	0.311
Non-smoking history	44 (37.6)	12 (41.4)	10 (37.0)	11 (35.5)	11 (36.7)		99 (87.6)	22 (91.7)	20 (76.9)	29 (90.6)	28 (90.3)	
Brinkman index[c] (cigarettes/day × yr)												
Mean	480	510	420	500	480	0.367	340	340	540	210	260	0.255
SD	360	370	350	370	360		330	390	410	260	230	

Note: The cohort consisted of 577 households, follow-up was completed for 502 of these. This table shows characteristic of members of the 502 households.

[a]Personal exposures were as follows: exposure group 1: 22.4 to 43.5 m^{-3}; exposure group 2: 43.5 to 91.8 m^{-3}; exposure group 3: 91.8 to 211.2 m^{-3}; and exposure group 4: 211.2 to1586.8 m^{-3}.

[b]Cumulative exposure = relative asbestos exposure concentration (m^{-3}) × exposure duration (yrs).

[c]Brinkman index value for persons with smoking history as of January 1992.

TABLE 2 Cause-specific Standardized Mortality Ratios (SMRs) for Residents Living Near the Hashima Asbestos Manufacturing Plant

Underlying Cause of Death	Chapter in ICD 10	Men				Women			
		O[a]	E[b]	SMR[c]	95%CI	O	E	SMR	95%CI
All causes		117	131.6	0.89	0.74–1.07	113	93.4	1.21	0.997–1.45
Infections	A, B	2	2.8	0.71	0.09–2.55	1	2.1	0.48	0.01–2.67
Neoplasms	C, D00–D48	40	47.8	0.84	0.60–1.14	30	28.2	1.06	0.72–1.52
Malignant neoplasm	C00–C97	40	46.7	0.86	0.61–1.17	29	27.4	1.06	0.71–1.52
Lip, oral cavity, and pharynx	C00–C14	1	0.9	1.06	0.03–5.92	0	0.3	0.00	0.00–11.8
Oesophagus	C15	1	2.3	0.44	0.01–2.45	0	0.4	0.00	0.00–10.3
Stomach	C16	1	8.5	0.12	0.00–0.66	3	4.2	0.72	0.15–2.11
Colon and rectum	C18–C20	4	5.1	0.78	0.21–1.99	8	3.8	2.13	0.92–4.20
Liver	C22	5	6.4	0.79	0.26–1.83	1	2.4	0.41	0.01–2.28
Gallbladder and biliary tract	C23–C24	0	1.8	0.00	0.00–2.06	1	1.9	0.54	0.01–2.99
Pancreas	C25	0	2.8	0.00	0.00–1.33	2	2.1	0.97	0.12–3.52
Lung and trachea	C33–C34	22	10.2	2.15	1.35–3.25	5	3.4	1.47	0.48–3.42
excluding cases with occupational asbestos exposure		15	10.2	1.46	0.82–2.41	4	3.4	1.17	0.32–3.00
excluding cases with occupational asbestos and silica exposure		13	10.2	1.27	0.68–2.17	4	3.4	1.17	0.32–3.00
Skin	C43–C44	0	0.1	0.00	0.00–28.9	1	0.1	9.81	0.25–54.6
Breast	C50	0	0.02	0.00	0.00–197	2	2.3	0.87	0.10–3.13
Uterus	C53–C55	—	—	—		2	1.2	1.60	0.19–5.79
Prostate	C61	1	1.8	0.56	0.01–3.12	—	—	—	
Bladder	C67	2	0.8	2.45	0.30–8.86	0	0.3	0.00	0.00–11.3
Central nervous system	C70–C72, C75.1–C75.3	2	0.2	8.63	1.04–31.2	1	0.2	5.86	0.15–32.6
Leukemia	C91–C95	0	1.0	0.00	0.00–3.62	1	0.7	1.52	0.04–8.46
Other malignant neoplasm		1	4.6	0.22	0.01–1.20	2	4.2	0.48	0.06–1.73
Endocrine	E	5	2.3	2.13	0.69–4.97	4	2.0	2.00	0.54–5.11
Nervous system	G	1	1.3	0.74	0.02–4.13	3	1.1	2.68	0.55–7.84
Circulatory system	I	33	36.2	0.91	0.63–1.28	39	32.0	1.22	0.87–1.66
Respiratory system	J	23	18.0	1.27	0.81–1.91	11	11.6	0.95	0.47–1.70
Digestive system	K	5	5.6	0.89	0.29–2.08	5	3.6	1.38	0.45–3.22
Musculoskeletal system	M	0	0.4	0.00	0.00–10.1	1	0.7	1.46	0.04–8.13
Genitourinary system	N	2	2.4	0.82	0.10–2.96	3	2.5	1.20	0.25–3.50
Symptoms/signs/findings	R	0	1.8	0.00	0.00–2.08	4	2.6	1.52	0.41–3.90
External causes	V, W, X, Y00–Y89	6	11.7	0.51	0.19–1.12	12	5.7	2.10	1.09–3.67

[a]O = observed deaths.
[b]E = expected deaths.

subjects to experience significantly higher respiratory disease mortality were men in exposure group 2. Of the eight respiratory disease cases, one died from pneumoconiosis, an occupational disease. When we excluded this case from the analyses, the mortality decreased to a non-significant level (SMR, 2.07; 95%CI, 0.83–4.27).

Comparison between Deceased Persons from Lung Cancer and Other Causes

Table 4 compares birth year, first exposure year, age at first exposure, exposure intensity, and smoking status between persons whose COD was lung cancer and those who died from other causes. In this analysis, lung cancer cases with occupational asbestos exposure were excluded. We did not detect significant differences in birth year, first exposure year, or age at first exposure, but there were significantly higher proportions in the most highly exposed group (group 4) of lung cancer deaths for both genders. The proportion of smoking history was significantly higher in men who had died from lung cancer, though their corresponding Brinkman indices were not higher.

DISCUSSION

The area enclosed by the black line in Figure 1 represents the study area. As mentioned, it corresponds to

TABLE 3 Mortalities of All Causes, Lung Cancer, and Circulatory and Respiratory Diseases in Residents Classified by Relative Asbestos Exposure Concentration

	Exposure Group 1[a]				Exposure Group 2				Exposure Group 3				Exposure Group 4			
Cause of Death	**O[b]**	**E[c]**	**SMR[d]**	**95%CI**	**O**	**E**	**SMR**	**95%CI**	**O**	**E**	**SMR**	**95% CI**	**O**	**E**	**SMR**	**95%CI**
All causes																
Men	29	26.5	1.10	0.73–1.57	27	28.1	0.96	0.63–1.40	31	40.4	0.77	0.52–1.09	30	36.6	0.82	0.55–1.17
Women	24	24.5	0.98	0.63–1.46	26	22.3	1.17	0.76–1.71	32	24.7	1.30	0.89–1.83	31	22.0	1.41	0.96–2.00
Lung cancer																
Men	5	2.1	2.44	0.79–5.69	2	2.3	0.89	0.11–3.20	6	3.2	1.86	0.68–4.05	9	2.7	3.31	1.51–6.28
Women	0	0.9	0.00	0.00–4.29	1	0.8	1.28	0.03–7.15	0	0.9	0.00	0.00–4.00	4	0.9	4.70	1.28 –12.0
Lung cancer without occupational asbestos exposure																
Men	2	2.1	0.97	0.12–3.52	1	2.3	0.44	0.01–2.47	4	3.2	1.24	0.34–3.18	8	2.7	2.94	1.27–5.79
Women	0	0.9	0.00	0.00–4.29	1	0.8	1.28	0.03–7.15	0	0.9	0.00	0.00–4.00	3	0.9	3.52	0.73–10.3
Lung cancer without occupational asbestos and silica exposure																
Men	2	2.1	0.97	0.12–3.52	1	2.3	0.44	0.01–2.47	3	3.2	0.93	0.19–2.72	7	2.7	2.57	1.03–5.30
Women	0	0.9	0.00	0.00–4.29	1	0.8	1.28	0.03–7.15	0	0.9	0.00	0.00–4.00	3	0.9	3.52	0.73–10.3
Circulatory diseases																
Men	9	7.1	1.27	0.58–2.41	9	7.4	1.21	0.55–2.30	7	11.3	0.62	0.25–1.28	8	10.4	0.77	0.33–1.51
Women	9	8.5	1.06	0.48–2.01	8	7.7	1.04	0.45–2.05	13	8.4	1.55	0.82–2.65	9	7.4	1.21	0.56–2.30
Respiratory diseases																
Men	4	3.3	1.21	0.33–3.10	8[e]	3.4	2.37	1.02–4.67	7	5.8	1.20	0.48–2.47	4	5.5	0.72	0.20–1.85
Women	2	3.2	0.63	0.08–2.27	3	2.8	1.07	0.22–3.13	4	3.0	1.32	0.36–3.37	2	2.6	0.78	0.09–2.80

[a]Personal exposures were as follows: exposure group 1: 22.4 to 43.5 m^{-3}; exposure group 2: 43.5 to 91.8 m^{-3}; exposure group 3: 91.8 to 211.2 m^{-3}; and exposure group 4: 211.2 to1586.8 m^{-3}.
[b]O = observed deaths.
[c]E = expected deaths .
[d]SMR = standardized mortality ratio.
[e]One of the eight cases died from pneumoconiosis, an occupational disease, and excluding this case, the mortality decreased to non-significant level (SMR = 2.07, 95%CI: 0.83–4.27).

TABLE 4 Comparison Between Deceased Persons from Lung Cancer without Occupational Asbestos Exposure and Other Causes

	Men			Women		
	Cause of Death			Cause of Death		
	Lung Cancer[a]	Other Causes	*p*-value	Lung Cancer[a]	Other Causes	*p*-value
Number	15	95		4	108	
Year of birth (n (%))						
1905–1929	8 (53.3)	54 (56.8)	0.799	4 (100)	78 (72.2)	0.218
1930–1986	7 (46.7)	41 (43.2)		0 (0.0)	30 (27.8)	
Year of first exposure (n (%))						
1943–1959	10 (66.7)	56 (58.9)	0.571	3 (75.0)	63 (58.3)	0.506
1960–1991	5 (33.3)	39 (41.1)		1 (25.0)	45 (41.7)	
Age at first exposure (n (%))						
0–29	11 (73.3)	53 (55.8)	0.200	1 (25.0)	50 (46.3)	0.401
≥ 30	4 (26.7)	42 (44.2)		3 (75.0)	58 (53.7)	
Exposure intensity (n (%))						
Exposure group 4	8 (53.3)	21 (22.1)	0.011	3 (75.0)	27 (25.0)	0.027
Exposure groups 1 to 3	7 (46.7)	74 (77.9)		1 (25.0)	81 (75.0)	
Smoking status (n (%))						
Smoking history	14 (93.3)	53 (55.8)	0.006	0 (0.0)	14 (13.0)	0.441
Non-smoking history	1 (6.7)	42 (44.2)		4 (100)	94 (87.0)	
Brinkman index[b] (Mean (cigarettes/day × yr))	800	720	0.499	—	480	—

[a]Excluding lung cancer deaths with occupational asbestos exposure.
[b]Brinkman index value for persons with smoking history as of January 1992.

eight districts surrounding the asbestos manufacturing plant that participated in our study via their community associations. Of the 11 district community associations that were invited to join the study, the three that did not participate were located on the north side of the study area and, importantly, not adjacent to the plant. So we believe that selection bias due to their nonparticipation was probably not significant.

Our study subjects were those who had lived in the study area as of January 1, 1992, and either continued to reside there or had at least one of their household members who resided there until June 30, 2007. One hundred sixty-two of the 739 households who resided in the study area as of January 1992 were excluded from our research because by June 2007 all household members had either moved away or died. Of the 162 households, 36, 43, 35, and 48, respectively, were located in areas corresponding to exposure groups 1 to 4. These numbers suggest that these houses were distributed throughout the entire study area and that the household members' asbestos exposure resembled that of the study subjects. If the death rate of members of the households whose members had all moved out had been higher than that of our study cohort, their exclusion would have caused our SMRs to be underestimated, and vice versa. Because the community associations knew of no households who had moved from the study area because of health problems, the first scenario described above, that of our SMRs being underestimated, was unlikely. At the very least, a dramatic understatement of risk was very improbable. Another phenomenon that could have caused our mortality estimate to be mistakenly low would be the death of all members in most of the 162 excluded households. This situation also was very unlikely because of our relatively short follow-up period (15.5 years).

Of the 577 study households, 13% (n = 75) did not respond to our survey despite repeated requests. As to whether these subjects differed from members of the 502 participating households, we know that these nonresponders were fairly evenly distributed among the four exposure groups. This phenomenon allayed our concern that this group differed from study participants in some way or ways that would have been relevant to the exposure or disease being studied.

We considered the roster of household members (spouses, parents, grandparents, children, and grandchildren) reliable because it was provided by the head-of-household and included simply relatives who lived together as of January 1992. Moreover, the data that we requested about each resident relative was very basic: name, sex, date of birth, date of death, first year residing in the area, smoking status, and occupational and residential histories. A third factor that suggests that the information provided was highly credible was that for deceased persons, we used death certificates to verify the

questionnaire data. These certificates listed the same demographics, but did not list either first year residing in the area or smoking status. Furthermore, we confirmed that both the gender and five-year age distributions of the study subjects were similar to those of Hashima's population in 1990—collateral evidence that the data was both reliable and complete. However, because the family representatives provided information about smoking amount and duration for only 63% of those with smoking histories, we considered the mean Brinkman index calculation to be a rough estimate.

It is difficult to verify that a given person did not experience any exposure to asbestos in the workplace over his/her entire life. In the current study, for lung cancer deceased persons, the head-of-household provided an entire lifetime chronological table of occupational history, and on the basis of both the occupational history and a list of job categories with potential asbestos exposure, an industrial hygienist assessed the possibility of a study subject's job-related exposure. Given the intensive data collection and its assessment by an industrial hygienist, we believe that, for persons classified as non-exposure, even if the persons experienced some exposure to asbestos in the workplace, the intensity was probably low.

Smoking is a major risk factor for lung cancer. In Japan, 39% of men and 11% of women aged 20 and older smoked in 2005,[33] percentages that resemble those of our cohort (39% and 5%). Consequently, we believe that using the sex- and age-specific national mortality rates to estimate expected deaths in our cohort was appropriate.

In 1972, the Japanese government implemented a law regulating industrial asbestos sites. It mandated that owners of such plants install local exhaust ventilation to protect employees from occupational exposure and dust collectors to prevent the outside environment from plant emissions. Even if this requirement had triggered immediate compliance, more than half of this study cohort was likely exposed to plant asbestos emissions because they had lived in the area before that year. As stated above, Hashima's municipal government conducted a medical examination of 298 residents who had lived in the city prior to 1977. This exam revealed that, of 161 residents who had neither occupational nor domestic exposure to asbestos, 41 (26%) had radiographic evidence of pleural plaques.[25] Accordingly, these residents must have been exposed to asbestos in their environment.

In 2000, the city of Hashima occupied 53.6 square kilometers and had a population of 64,700 (31,700 men and 33,000 women). Between 1992 and 2006, 325 men and 99 women died from lung cancer in the city.[34,35] Based on sex-, age-, and calendar-year-specific lung cancer mortality rates for the Japanese population, SMRs were 1.23 (95%CI, 1.11–1.37) for men and 1.06 (95%CI, 0.87–1.29) for women. Comparing these SMRs with those of our cohort—2.15 (95%CI, 1.35–3.25) for men and 1.47 (95%CI, 0.48–3.42) for women—suggests that the lung cancer mortality in the study area was higher than that of the city.

Excluding lung cancer cases with occupational asbestos exposure reduced SMRs to 1.46 (95%CI, 0.82–2.41) in men and 1.17 (95%CI, 0.32–3.00) in women. In this situation, cases with occupational asbestos exposure were excluded from the observed number, but not from the number expected in the Japanese population. Therefore, these SMRs were actually underestimated.

If individuals with occupational asbestos exposure were excluded from the observed lung cancer cases, the analyses based on relative asbestos concentrations yielded the highest SMRs for exposure group 4: 2.94 (95%CI, 1.27–5.79) in men and 3.52 (95%CI, 0.73–10.3) in women. The male SMR value was statistically significant, but the female SMR value was not, probably because the latter group's person-years of observation were too small to detect significant excess lung cancer deaths. Furthermore, when cases with occupational asbestos or silica exposure were excluded, the mortality risk remained significantly higher for men in this exposure category. Circulatory disease SMRs were not significant for any asbestos exposure group, nor were SMRs for respiratory diseases once the man who died from pneumoconiosis was excluded from the exposure group 2 analysis. These two findings—that only residents who experienced the highest asbestos exposure (group 4) experienced significant elevated lung cancer mortality risk, despite nearly uniform smoking status among the four groups, and that residents in none of the four exposure areas had higher mortality from other diseases—suggest that neighborhood asbestos exposure caused their lung cancer deaths.

The analysis of deceased subjects showed that birth year, first exposure year, and age at first asbestos exposure were not significantly different between lung cancer deaths and those due to other causes. However, we found that the proportion of the highest exposure group had significantly greater lung cancer mortality for both genders (Table 4). This finding suggests that the intensity of the neighborhood asbestos exposure was an important factor for developing lung cancer. We also showed that the proportion of individuals with smoking history was significantly higher in persons who died from lung cancer for men, suggesting tobacco as an important cause of their disease. These findings confirm results from earlier research establishing that asbestos and tobacco act synergistically as lung carcinogens.[36]

Some studies have examined lung cancer mortality in people living near asbestos plants and mines.[16,20–23] However, only one of these investigations excluded cases with occupational and/or domestic asbestos exposure.[22] In that study, researchers calculated male

and female lung cancer mortality in an extensive area around an asbestos cement plant. After eliminating plant workers and their spouses from the lung cancer death cases, they did not detect a significant increase in lung cancer mortality. Attempting to reconcile this finding with those in our study, the size of the study area provides a credible explanation. Quite simply, designating a relatively large area around the asbestos plant created a study area that was too large to detect a significant increase in lung cancer mortality. Including residents who lived ≥2.5 km from the exposure source in the data analysis obscures or dilutes the more substantial risk of subjects residing near the plant. Similarly, we could not detect significant lung cancer mortality in our study area as a whole. But, by dividing the area into smaller zones according to relative asbestos concentration, we observed a significant excess lung cancer mortality risk associated with the highest exposure concentration.

The present study did not observe mesothelioma deaths in the study cohort. This is probably because of the relatively small person-years of observation. If one mesothelioma death had been observed in this study, the SMRs would be 8.33 in men and 25.0 in women, based on the cause-specific death rate in the Japanese population. One woman who lived in the highest asbestos exposure area (group 4) and who did not work with asbestos died from pleural mesothelioma in 1989.[26] Because we designated the follow-up period as 1992 to 2007, this death could not qualify as a study case. Another women who worked at a public hospital located in the area with the highest relative asbestos concentration was diagnosed with pleural mesothelioma in 2005.[27] Again, this person did not qualify as a subject because she lived outside of the study area as of 1992. In 2006, another individual, a man who worked at a woolen mill located in exposure group 4, was diagnosed with pleural mesothelioma.[37] This man also did not qualify as a subject because he lived outside of the study area as of 1992. Though technically not part of our study cohort, these cases nevertheless raise concerns about mesothelioma risk in this area.

CONCLUSION

This study showed that in the vicinity of the Nichias asbestos plant in Hashima, Japan, lung cancer mortalities without occupational asbestos exposure were the highest in the most highly exposed neighborhoods for both men and women, and that the male mortality was significantly higher than the gender-specific national reference population. Our investigation is the first study to suggest significantly higher lung cancer mortality associated with neighborhood asbestos exposure after excluding cases with occupational and domestic exposure. Our findings—and their comparison with similar investigations—help inform and advance the study of environmental exposures. In evaluating health risks associated with environmental asbestos exposure, it is essential to identify areas of high asbestos concentration in order to accurately evaluate associated lung cancer risk.

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