

Mapping the Risk of Mesothelioma Due to Neighborhood Asbestos Exposure

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Rationale: Little is known about neighborhood exposure to asbestos and mesothelioma risk among residents around an industrial source of asbestos.

Objectives: To investigate the magnitude of the risk among residents by asbestos exposure levels and to determine the range of the area affected by asbestos.

Methods: We calculated standardized mortality ratios of mesothelioma from 1995 to 2006 among the estimated population at risk that lived around a former large asbestos cement pipe plant in Amagasaki City, Japan, between 1957 and 1975, the time when the plant had used crocidolite and chrysotile. The distance between the plant and homes and relative asbestos concentrations obtained by diffusion equations involving meteorological conditions were used to determine asbestos exposure levels among residents.

Measurements and Main Results: We identified 73 mesothelioma deaths of 35 men and 38 women who had no occupational exposure to asbestos. Among persons who had lived within a 300-m radius of the plant, the standardized mortality ratio of mesothelioma was 13.9 (95% confidence interval, 5.6–28.7) for men and 41.1 (95% confidence interval, 15.2–90.1) for women. When the study area was divided into five regions by relative asbestos concentration, standardized mortality ratios of mesothelioma declined, for both sexes, in a linear dose-dependent manner with concentration. The regions with a significantly elevated standardized mortality ratio reached 2,200 m from the plant in the same direction in which the wind predominantly blew.

Conclusions: Neighborhood exposure to asbestos can pose a serious risk to residents across a wide area.

Keywords: relative asbestos concentration; crocidolite; environmental exposure; pleural mesothelioma

On the basis of a case series analysis of 33 patients with pleural mesothelioma, Wagner and coworkers (1) first reported, in 1960, a strong relationship between mesothelioma and exposure to crocidolite, including occupational, paraoccupational, and neighborhood exposures. Thereafter, several epidemiologic studies have reported on mesothelioma among residents with neighborhood exposure to asbestos from industrial activities (2–12). Asbestos has been used widely since the early 20th century, and many active and closed factories worldwide that handled asbestos and asbestos-containing products could have spread asbestos in surrounding communities.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There are few studies on the range of the area affected by neighborhood exposure to asbestos of industrial origin. Residential distance correlates with an increased risk of mesothelioma. However, meteorological factors have not been considered.

What This Study Adds to the Field

A dose-response relation, involving meteorological conditions, was observed between the risk of mesothelioma and relative asbestos concentrations. The area with a significantly increased risk reached 2,200 m from an emission point of asbestos.

To interpret a causal inference about mesothelioma encountered among residents and to protect the community from asbestos-related health hazards, public health professionals and policymakers would like to know the size and shape of at-risk neighborhoods. This information is available from few studies (2, 9–11), which investigated relations between residential distance and mesothelioma deaths. However, they did not consider meteorological factors, such as wind direction, that can influence diffusion of asbestos fibers from a point of source.

In Japan, a newspaper article published on June 29, 2005 (13), reported that five residents who had lived near a now-closed asbestos cement pipe plant (called “the plant” hereafter) in Amagasaki City, Hyogo Prefecture, developed pleural mesothelioma. The plant used crocidolite and chrysotile between 1957 and 1975. These deaths attracted much social concern, and the mass media covered specific and general asbestos-related problems daily afterwards. Kubota Corporation, a major machinery maker that ran the plant, established in April 2006 a compensation system for residents (14) who lived or worked within a 1-km radius of the plant when it used asbestos, developed asbestos-related diseases including mesothelioma, and were not exposed to asbestos occupationally. The company pays 25 to 46 million yen (\$220,000–420,000) per person to eligible residents and their bereaved families. A total of 164 residents with mesothelioma have applied for the compensation program as of April 2007, and most applicants have been compensated.

On the basis of these 164 cases, we describe here the epidemiologic features of mesothelioma due to neighborhood exposure to asbestos, we determine the risk of mesothelioma related to residential distance from the plant by methods described in previous studies (2, 9–11), and we estimate the range of the area affected by asbestos after taking account of meteorological conditions. We have also investigated the relationship between estimated exposure and risk of mesothelioma in the community.

Some of the results of this study have been previously reported in the form of an abstract (15).

METHODS

Subjects

The initial study population consisted of 162 of 164 residents with mesothelioma who had contacted the agent of Kubota Corporation by the end of April 2007 and for whom consent to our interview study was obtained (138 relatives of deceased subjects and 24 subjects under treatment). This study was approved by the Ethics Committee of Nara Medical University (Kashihara, Japan).

Data Collection and Calculation of Relative Asbestos Concentration

The interviewees were requested to bring official documents to certify the diagnosis of mesothelioma, occupational history, and place of residence. We obtained the date of the initial subjective symptom of mesothelioma and confirmed the diagnosis by reviewing the subject's medical charts when necessary. On the basis of both job descriptions provided by interviewees and a list of 19 occupational groups with 57 job categories that can lead to asbestos exposure (16), we decided whether the subject had a chance to have been exposed to asbestos at work. Possibilities of paraoccupational exposure were assessed by inquiring about occupations of the spouse, parents, and other household members. We defined each subject's exposure point to asbestos from the plant as the distance from (1) the house where the subject had lived for at least 1 year between 1957 and 1975 or (2) the place where the subject worked, whichever was the closest.

Because actual concentrations of airborne asbestos fibers in the surroundings of the plant, during the period when crocidolite was used, were unknown, we estimated "relative asbestos concentrations" (unit, m^{-3}) in each of 2,500 grid units (each grid unit, $100 \text{ m} \times 100 \text{ m}$). Briefly, the method assumed that an emission point of asbestos was at the center of the plant premises and used diffusion equations that account for meteorological conditions (17–20). We considered that airborne asbestos emitted from the plant was the sole industrial source of exposure among study subjects (*see* DISCUSSION).

Additional details are provided in the online supplement.

Data Analysis

To express the risk of death from mesothelioma, we calculated the ratio of the observed deaths to the expected deaths, which is the standardized mortality ratio (SMR). Observed deaths in our SMR analysis were those deaths that occurred from January 1, 1995 to December 31, 2006, when the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10), which first has a rubric specific for mesothelioma (C45), was in effect in Japan. Expected deaths in each year of 1995–1997, 1998–2002, and 2003–2006 were obtained by multiplying a sex- and 5-year age-specific population at risk in 1995, 2000, and 2005 by the corresponding national mortality of mesothelioma in 1995, 2000, and 2005, respectively. The population at risk as of 1975 was estimated on the basis of data from the city census in 1975 (21): 220,809 in the area within a 1,500-m radius from the center of the plant and 280,604 in the area whose relative asbestos concentration was above 2 m^{-3} . Additional details are provided in the online supplement.

We calculated 95% confidence intervals of SMRs, using the exact probabilities of the Poisson distribution (22). Multiple comparisons of average values among several groups were performed by one-way analysis of variance followed by Dunnett's procedure (23). The relation between relative asbestos concentration and the SMR of mesothelioma was evaluated by linear regression analysis (23). All statistical tests were conducted with SPSS version J11.5 for the PC (SPSS, Inc., Chicago, IL).

RESULTS

As shown in Figure 1, 121 of the 162 study subjects were judged as not having been exposed to asbestos directly or indirectly at work. Twelve of the 121 subjects worked at a location closer to the plant than their residence was, and the other 109 had no chance of occupational exposure to asbestos and had lived for at least 1 year near the plant when it used crocidolite. We then eliminated

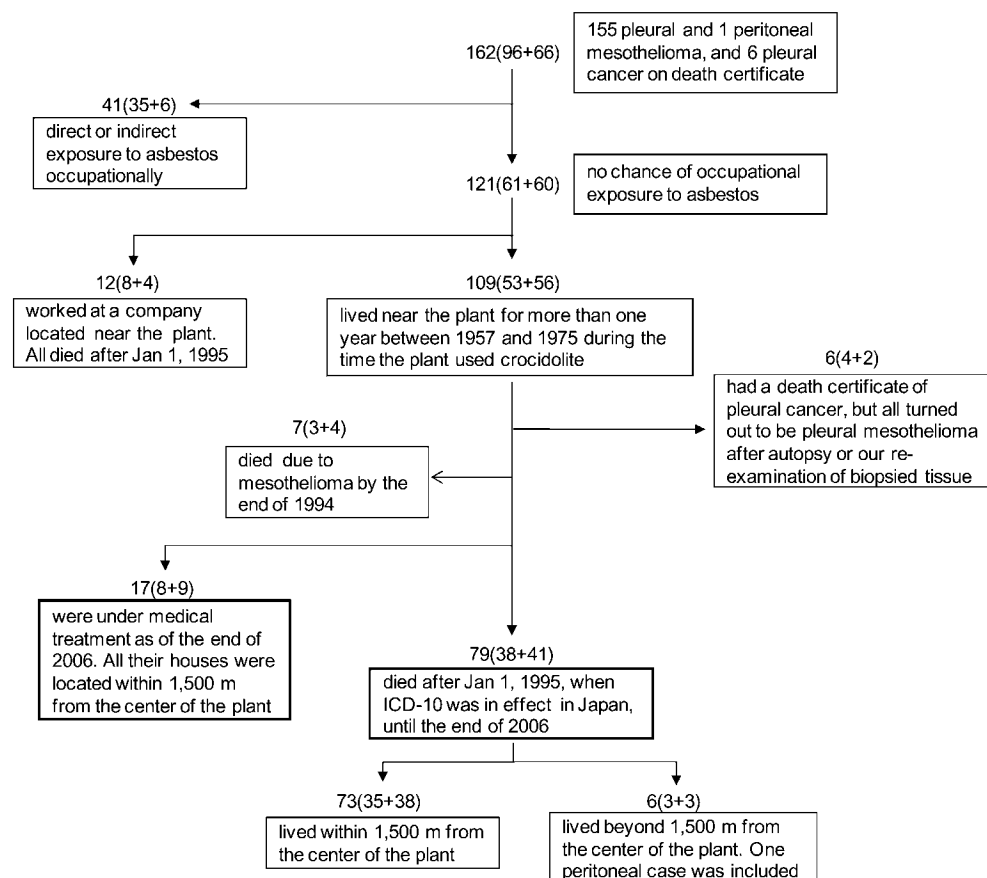


Figure 1. Study subjects by occupational, residential, and vital status. Figures indicate the number of people (men and women). The two boxes with bold outlines show the subjects selected for further analysis. Seven deaths that occurred before the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10), was in use (i.e., before 1995) were excluded for standardized mortality ratio (SMR) analysis because the expected deaths resulting from mesothelioma may be calculated on the basis of national mortality only after the enforcement of ICD-10, which was the first to have a specific rubric for mesothelioma (C45).

six subjects whose diagnosis was pleural cancer on the death certificate but turned out to be mesothelioma, to maintain comparability with the expected deaths calculated from national vital statistics. Further exclusion of seven deaths before the ICD-10 went into effect in Japan resulted in 79 mesothelioma deaths plus 17 patients under medical treatment for mesothelioma for further analysis. All of the 17 patients were diagnosed histologically. Of the 79 deaths, the diagnosis was confirmed by histology in 62 (78.5%), by cytology in 12 (15.2%), and by clinical findings including chest computed tomography scan in 5 (6.3%). Mean age at death was 56.9 years (SD 10.8) for men and 66.3 years (SD 11.8) for women. All 79 deceased subjects had pleural mesothelioma except for 1 patient with one peritoneal mesothelioma.

Table 1 summarizes the SMRs of mesothelioma and demographic characteristics of the 90 subjects who lived within a 1,500-m radius of the center of the plant. Residential distance was divided by intervals of 300 m. The 73 mesothelioma deaths showed a significantly increased SMR of 4.3 (95% confidence interval, 3.4–5.4). The highest SMR, 41.4 (95% confidence interval, 15.2–90.1), occurred among women who had lived within a 300-m radius of the center of the plant, and the SMR of women remained significantly elevated up to the group within 1,200 to less than 1,500 m. The SMRs of men were one-half or less than those of women. As for the women, the highest SMR among the men was found for those living within a 300-m radius of the plant; but only one other SMR for men, that is, the SMR of men living 300 to less than 600 m from the plant, was significantly elevated.

When data from the 73 deceased and 17 surviving subjects were combined, their residential period averaged 145 (range, 24 to 227) months, or 12.1 years, during the use of crocidolite in the plant. No statistically significant difference in time existed between men and women, but for both sexes the residential exposure in the 300-m radius group was 20 to 90 months shorter than

the exposure of the other distance groups. The latent period, defined as the time from the subject's first year living near the plant to the appearance of the initial symptom related to mesothelioma, varied from 265 to 595 months with an average of 520 months, that is, about 43.3 years. We found no significant differences in the latent period (1) between men and women or (2) among the groups by distance from the plant.

Figure 2 depicts relative asbestos concentrations classified into nine levels in each of the 100 m × 100 m grid units with places of residence of the 90 deceased and surviving subjects. We assumed the center of the plant premises was a single emission point of asbestos. The relative asbestos concentrations decrease rapidly as the distance from the plant increases. Also, grid units with higher concentrations occur more frequently to the south-southwest of the plant, coincident with the study area's predominant wind direction of blowing from the north-northeast (see Figure E1 in the online supplement). Mesothelioma case homes were scattered more north-south than east-west and more south than north relative to the plant. We identified three mesothelioma deaths (not depicted) among subjects who worked in a factory in a grid unit south of the plant whose relative asbestos concentration was the highest in the study.

Figure 3 illustrates regression lines of the SMR of mesothelioma among the deceased against relative asbestos concentrations. For this analysis, we determined five areas with the following relative asbestos concentration levels: 2–4.9 (3.2 on average), 5–9.9 (6.9), 10–19.9 (13.7), 20–49.9 (30.4), and 50–199.9 (89.8). This grouping was not done according to quintiles of asbestos exposure or population exposed, but the bands were defined so as to have at least five deaths and a high enough population at risk to allow a statistical analysis. (An area with a relative concentration of 200 m⁻³ or greater [Figure 2] was excluded from the analysis because it contained only the plant and the other big factories, but no residences. Also excluded was an

TABLE 1. STANDARDIZED MORTALITY RATIO OF 73 MESOTHELIOMA DEATHS AND DEMOGRAPHIC CHARACTERISTICS OF THE 73 DEATHS AND 17 PATIENTS UNDER TREATMENT BY SEX AND RESIDENTIAL DISTANCE FROM THE PLANT WITHIN A 1,500-METER RADIUS

Residential Distance from Plant (m)	Estimated Population at Risk as of 1975	No. of Deceased in 1995–2006	SMR (95% CI)	Age at Death (yr)	No. of Patients under Treatment	Total No. of Deceased Subjects and Subjects under Treatment	Residential Months at Risk	Latent Period (mo)
Men								
0 to <300	4,213	7	13.9 (5.6–28.7)	67.6 ± 10.1*	0	7	105 ± 58†	515 ± 55
300 to <600	17,963	12	5.6 (2.9–9.8)	52.6 ± 10.0	4	16	146 ± 58	526 ± 46
600 to <900	28,259	7	2.1 (0.8–4.3)	54.6 ± 9.7	2	9	125 ± 53	519 ± 49
900 to <1,200	27,891	4	1.2 (0.3–3.1)	57.9 ± 10.4	1	5	184 ± 50	520 ± 61
1,200 to <1,500	32,568	5	1.3 (0.4–3.0)		1	6		
Subtotal	110,894	35	2.6 (1.8–3.7)	57.3 ± 11.1	8	43	145 ± 60	521 ± 51
Women								
0 to <300	4,175	6	41.4 (15.2–90.1)	63.3 ± 9.8	3	9	98 ± 63‡	497 ± 105
300 to <600	17,804	7	11.3 (4.5–23.3)	66.7 ± 12.7	0	7	158 ± 55	511 ± 46
600 to <900	28,010	7	7.2 (2.9–14.8)	63.7 ± 10.0	3	10	187 ± 42	521 ± 67
900 to <1,200	27,646	8	8.3 (3.6–16.4)	64.9 ± 17.8	3	11	142 ± 78	526 ± 48
1,200 to <1,500	32,280	10	8.9 (4.3–16.4)	67.7 ± 9.2	0	10	144 ± 78	532 ± 32
Subtotal	109,915	38	9.9 (7.0–13.7)	65.5 ± 11.8	9	47	146 ± 69	518 ± 63
Total	220,809	73	4.3 (3.4–5.4)	61.6 ± 12.1	17	90	145 ± 64	520 ± 57

Definition of abbreviations: 95% CI = 95% confidence interval; SMR = standardized mortality ratio.

Vital status is as of December 31, 2006. Residential and latent period months were calculated for 73 deaths plus 17 patients under treatment.

* Significant difference ($P < 0.05$) in average between men living 0 to less than 300 m, and men living 300 to less than 600 m, from the plant by one-way analysis of variance followed by Dunnett's procedure.

† Significant difference ($P < 0.05$) in average between men living 0 to less than 300 m, and men living 900 to less than 1,500 m, from the plant by one-way analysis of variance followed by Dunnett's procedure.

‡ Significant difference ($P < 0.05$) in average between women living 0 to less than 300 m, and women living 600 to less than 900 m, from the plant by one-way analysis of variance followed by Dunnett's procedure.

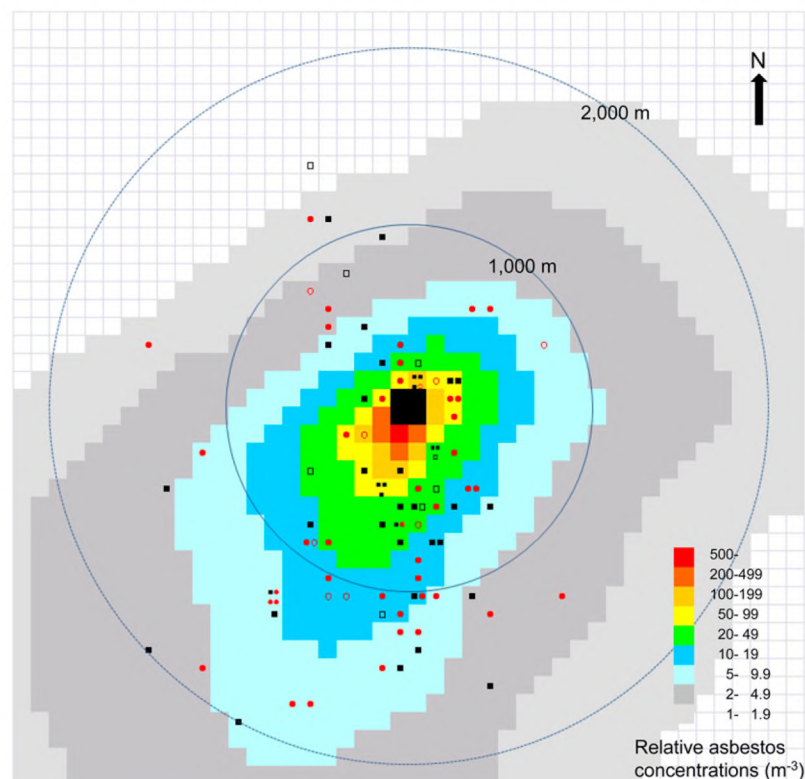


Figure 2. Distribution of relative asbestos concentrations in a grid consisting of 100 m $\times$ 100 m grid units, with places of residence indicated for 79 subjects who died of mesothelioma and 17 patients under medical treatment for mesothelioma. Relative asbestos concentrations were obtained by diffusion equations involving meteorological conditions in the study area. The large solid square represents the plant. The blue circles indicate 1,000- and 2,000-m radii from the plant's center. Solid black squares, dead male subjects; open black squares, living male patients; solid red circles, dead female subjects; open red circles, living female patients.

area with a concentration of less than 2 m^{-3} because the area was too wide to limit its boundary and, therefore, we were unable to enumerate the population at risk; four deaths [two men and two women] lived in that area.) The sex-specific SMR of each area was calculated and the relation between relative asbestos concentrations and these SMRs was investigated by linear regression analysis. As shown in Figure 3, the highest SMR, 47.7 (95% confidence interval, 20.8–105.7) occurred for women in the area that had the highest relative asbestos concentration. Significantly increased SMRs were found in the area with concentrations of more than 5 m^{-3} . The area reached about 2,200 m south-southwest and 900 m north-northeast from the plant's center (Figure 2). Although the SMR regression line of men is significantly less steep than that of women ($P < 0.05$), both lines show a linear dose-response relation between relative asbestos concentration and risk of mesothelioma. These results did not change after exclusion of 11 subjects who had died while living with household members who could have been exposed to asbestos at work (see Figure E2).

DISCUSSION

From 1957 to 1975, our study plant used an annual average of 4,670 tons of crocidolite and an annual average of 4,600 tons of chrysotile to produce cement pipes (24) (see Figure E3). The amount of asbestos used was about 5–10% of all asbestos imported to Japan in those years. According to local government information (25), none of the other 135 closed and current companies identified in Amagasaki City where asbestos products were made or used reported consuming more than 10 tons of crocidolite per year, far less than the amount used by the study plant. Packed raw asbestos transported to the plant by vehicle was separated by fluffing and then was sent upstairs through pneumatic ducts, collected, mixed with other materials to mold cement pipes, dried, and cut (24). The plant operated around the clock.

We believe that fluffed asbestos was emitted from the outlet of the ducts, dispersed into the surrounding air, and inhaled by neighborhood residents. Previous studies suggested that (1) transport of raw asbestos with a loosely attached cover (11, 26), (2) improper use of asbestos residuals (1, 11, 12) such as for thermal home insulation, gardening, and creating a hard pavement, and (3) playing on piles of asbestos (12) were other asbestos exposure routes in the environment around a plant. In our study,

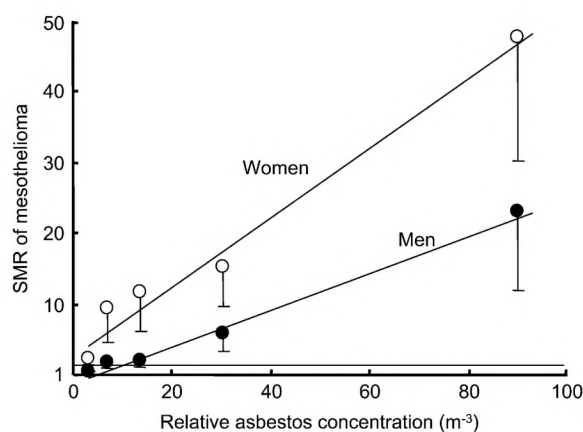


Figure 3. Dose-response relation between standardized mortality ratios (SMRs) of mesothelioma and relative asbestos concentration levels divided into five exposure groups. The regression lines are as follows: $y = 0.49 (0.36 \text{ to } 0.62) x + 3.09 (-2.44 \text{ to } 8.61)$ for 39 women and $y = 0.26 (0.22 \text{ to } 0.31) x - 0.89 (-2.83 \text{ to } 1.05)$ for 36 men. Figures in parentheses in the equations represent 95% confidence intervals of the slope and intercept. The vertical bar at each point shows the range of the lower 95% confidence interval of the SMR.

these routes were not found except for a single narrow 30-m-length road with asbestos residuals located 500 m southwest of the plant. We did not find naturally occurring asbestos, which can cause mesothelioma (27), in the study area, and houses were not constructed with asbestos-contaminated soil mixtures (28). In the study plant, 46 employees had mesothelioma in the past 20 years, and 40 had asbestosis or asbestos-related lung cancer (24). Mesothelioma, especially pleural mesothelioma, is highly specific to asbestos (29, 30). All these facts inspired us to investigate the occurrence of the disease in the study area under the assumption that the plant was the only emitting source of crocidolite, which has much greater carcinogenicity than chrysotile (31).

Our study interviewees were individuals or their families who voluntarily contacted the agent of Kubota Corporation to seek compensation for death or disease related to environmental exposure to asbestos. We could not enroll all deaths due to mesothelioma in the study area during the study period because no mesothelioma registry existed. Accordingly, a selection bias must exist. For example, deceased persons without relatives and people who were unaware of the Kubota event did not contact the compensation agent. Bias from such unreported cases would result in underestimation of the SMRs. We determined carefully whether or not the subjects had been exposed to asbestos at their workplace. However, misclassification was inevitable. The list of occupations (16) to which we referred includes all jobs with possible exposure to asbestos, which tends to make more false positives than false negatives, resulting in underestimation of the SMRs.

On the other hand, underestimation of the population at risk may lead to overestimations of the SMRs, but it is unlikely that large errors occurred in the population estimates and it is even less likely that such errors varied systematically with exposure.

The present study showed higher SMRs among women than men. We excluded cases with occupational exposure when counting observed deaths, but could not do so for expected deaths because no relevant data were obtained from the national vital statistics office. This bias also leads to underestimation of the SMRs. Such bias could be greater for men than for women because more men than women had been employed and therefore were exposed to asbestos occupationally. Consequently, our results show more directly for women than for men the effects of environmental asbestos exposure from the plant.

Few studies have been reported, to our knowledge, on the risk of mesothelioma in relation to the residential distance from an industrial source of asbestos. A significantly increased risk of mesothelioma was observed within half a mile of an asbestos factory in London (2), within 1,000 and 2,000 m of asbestos mines, asbestos factories, or shipyards in South Africa (9) and some European countries (10), respectively, and beyond 2,500 m of an asbestos cement factory in Italy (11). Our results on residential distance are consistent with these previous findings.

None of the previous studies considered meteorological conditions. Asbestos concentrations in the air surrounding the emission point depend on wind direction and velocity (32), which determine the direction and distance that asbestos fibers travel. Actually, relative asbestos concentration levels differed greatly in different directions from our study plant even when the distance from the plant was the same. For example, among women, the area with relative concentration levels showing significantly elevated SMRs extended as far as 2,200 m south-southwest of the plant, toward which the wind predominantly blew, but only 900 m in the opposite direction, north-northeast. Thus, a parameter including meteorological conditions is a better proxy as exposure dose than residential distance only, and it should be useful to investigate more accurately the effects of asbestos exposure among residents in communities.

When relative asbestos concentration was used as dose of asbestos exposure, a clear linear relation was observed for both sexes. Such relations have been established by epidemiologic findings in occupational settings (33), where asbestos exposure is higher than it is in neighborhoods. The present results suggest that the linear model can apply to settings, with much lower exposure levels, such as those resulting from environmental contamination.

Nearly 100 subjects with mesothelioma were identified as victims of neighborhood exposure in the present study. This number is one of the largest reported in studies of mesothelioma among residents around industrial sources of asbestos (1–12). Our subjects lived near the plant for 12 years on average, and developed the disease after a latency of 43 years on average. This duration of residential exposure is comparable to that of subjects who developed mesothelioma after living within half a mile of an asbestos factory in London (2) (14.4 yr on average) and is more than double that of subjects with mesothelioma who lived in the neighborhood of a crocidolite mine in Australia, 89% of whom, however, also lived with an asbestos worker (34).

Two features of our study cases are noteworthy. First, all subjects but one had pleural mesothelioma. In the plant itself, peritoneal mesothelioma occurred in 28 workers and pleural mesothelioma occurred in 18 workers (24). This contrast is consistent with knowledge that peritoneal mesothelioma occurs more often in persons exposed to higher levels of asbestos (35, 36). Second, workers exposed to asbestos occupationally may be younger at the time of death. Our subjects who died were 10 years younger (men) and 5 years younger (women) compared with all Japanese who died of mesothelioma (37). Because workers are not exposed to asbestos until they are actually working with it, whereas residents of areas polluted with asbestos are exposed from the time they start to live there, sometimes from birth (38), it is understandable that asbestos-related deaths occur at younger ages after residential exposure than after occupational exposure.

In conclusion, we believe the mesothelioma outbreak among residents was causally associated with asbestos, in particular crocidolite, that the plant had used, and that the affected area spread as far as 2,200 m from the center of the plant in a dose-dependent way. Public health policymakers, health professionals, and companies should recognize the serious risk to health of neighborhood exposure to asbestos across a wide area.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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