Association of mesothelioma deaths with cumulated neighborhood exposures due to a large-scale asbestos cement plant in *Amagasaki City, Japan*: A nested case-control study

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Abstract

Background: Although a causal relationship between mesothelioma and asbestos exposure is well known, few studies have shown a relationship to non-occupational exposure, including neighborhood exposure, most likely because of the large effect size of occupational exposure. The aim of this study was to quantify the risk of malignant mesothelioma death associated with neighborhood asbestos exposure due to a large-scale asbestos-cement (AC) plant in Amagasaki, Japan, by properly adjusting for occupational exposure.

Methods: We conducted a nested case-control study in which a fixed population of 143,929 residents who had been living in Amagasaki City between 1975 and 2002 were followed from 2002 to 2015. All 133 cases and 403 matched controls were interviewed about their occupational, domestic, household, and neighborhood asbestos exposures. Odds ratios (ORs) for mesothelioma death associated with neighborhood exposure were estimated by a conditional logistic-regression model that adjusted for other asbestos exposures. We adopted cumulative indices that considered residence-specific asbestos (crocidolite) concentrations and durations during the potential exposure period of 1957-1975 to evaluate individual neighborhood exposures.

Results: There was an increasing, dose-dependent risk of mesothelioma death associated with neighborhood exposure, demonstrated by ORs in the highest quintile category that were 21.4 (95% CI: 5.8 - 79.2) for all, 23.7 (95% CI: 3.8 -147.2) for males, and 26.0 (95% CI: 2.8 - 237.5) for females, compared to the lowest quintile, respectively. These results clearly demonstrated no substantial differences between males and females in relation to the magnitude of risk from neighborhood exposure.

Conclusions: By adjusting for occupational and other asbestos exposures, a dose-dependent relationship was demonstrated between mesothelioma death and neighborhood asbestos exposure from a large-scale AC plant. Our findings suggest that the risk of mesothelioma death associated with neighborhood exposure persists and will not be diminished for many years, even though it has been decades since the AC plant closed.

Background

Although the causal relationship between mesothelioma and asbestos exposure is well known, most of the convincing evidence has been obtained in occupational contexts [1–3], and few studies have shown whether the environmental exposures, including neighborhood, domestic, and household exposure, would quantitatively elevate the risk of mesothelioma death [4–7]. In Amagasaki City on 29 June 2005, a newspaper report documented five cases of mesothelioma among residents around a former large-scale asbestos-cement (AC) plant (Kubota Kanzaki Factory), which was considered the largest asbestos consumer in Japan [8], and the incident became known as “the Kubota Shock”. Actually, during the period 1957–1975, a large amount of asbestos (annual average per year: 4,670 tons of crocidolite and 4,600 tons of chrysotile), corresponding to approximately 5 to 10% of all asbestos imported to Japan, was used in the AC plant, and no other plants that used more than 10 tons of crocidolite per year were identified as asbestos-related companies in Amagasaki City [9, 10].

In our previous study in 2008, we demonstrated a clearly dose-dependent remarkably increased mortality of malignant mesothelioma associated with the simulated distribution of airborne asbestos due to the AC plant in Amagasaki City, taking into account meteorological conditions at that time [11]. Moreover, by using spatial epidemiological mapping at the municipality level across Japan, Nakaya revealed distinctive geographical concentrations of elevated risk of mesothelioma death, especially in women, in several cities including Amagasaki City, during the latest observation period between 2010 and 2014 [12]. Zha, et al. also demonstrated that standardized mortality ratios (SMRs) for malignant mesothelioma compared to nation-wide mortalities were 6.75 for males and 14.99 for females between 2002 and 2015 in Amagasaki City [13].

In general, we know that a finding of significant occupational asbestos exposure associated with mesothelioma deaths could largely affect the assessment of other asbestos-related exposures, even in a multivariate analysis with an adequate adjustment. On the other hand, excluding occupational exposure entirely might be a major cause of gender differences in evaluation of mortality rate ratio because of underestimation, especially in male subjects.

The aim of this nested case-control study was to determine the quantitative association between neighborhood asbestos exposure and mesothelioma deaths, taking into account geographical distributions of the relative concentration of airborne asbestos fibers due to a large-scale AC plant and also considering durations at each residential place in Amagasaki City.

Methods

We conducted a population-based nested case-control study within the long-term resident cohort in Amagasaki City. The long-term resident cohort, who had been continuously living in Amagasaki City before 1975 and at least until the beginning of 2002, were followed from 1 January 2002 to 31 December 2015 for death or outmigration status using the Basic Resident Records in our previous study[13]. We observed 143,929 residents aged 40 years or more at baseline. The cause of death, mesothelioma, was identified as code C45 according to the International Classification of Disease, 10th Revision (ICD-10), using the National Vital Statistics. The Amagasaki City government provided a data set of malignant mesothelioma deaths that included both pleural and peritoneal mesothelioma between 2002 and 2015 with completed interviews regarding occupational and non-occupational histories related to asbestos exposures, which was obtained from the surveillance based on support by the Ministry of Environment.

The cumulated number of mesothelioma deaths was 379, including 13 peritoneal and 366 pleural mesothelioma deaths between 2002 and 2015 in the entire city, which were target subjects for the interview survey by the Amagasaki City government (Fig. 1). Of these, 110 death cases were excluded because no bereaved families existed or they had moved out of the city. The remaining 269 death cases were contacted for interview and 102 refused or did not respond, resulting in 167 death cases with completed interviews. Of these, 133 death cases met criteria of the Amagasaki City long-term resident cohort and were used as the nested cases. Case interviews of the bereaved families, with informed consent, were conducted by well-trained nurse interviewers employed by the government between 2002 and 2015.

Control candidates were randomly selected from the long-term resident cohort populations matched by sex and age (birth date ± 12 months) and alive on the date of death of corresponding case. Furthermore, three or more matched controls with completed interviews were required per case. To obtain three matched controls per case, 40 candidates per case were randomly extracted from the Amagasaki City long-term resident cohort. Of 5,320 candidates, 1,129 candidates were excluded because they had no family members or had moved out of the cohort. The municipal government sent requests to 4,191 subjects with identified addresses in Amagasaki City to obtain consent for their cooperation. After excluding 1,471 subjects who did not respond, 1,575 subjects who refused, and 70 subjects who responded as under consideration, we sent the individual questionnaires and consent forms for interview in a closed document to 1,075 subjects who had given their permission to be contacted. The interviews were then conducted in the order of consent, by home visit or telephone, and were terminated when at least three controls per case had been secured. Therefore, excluding 54 subjects for whom interviews were canceled before sending questionnaires, we sent a total of 1,021 questionnaires and obtained 403 (39.5%) completed interviews with consents (Fig. 1).

A total of 133 cases and 403 matched controls in the Amagasaki City long-term resident cohort were confirmed as eligible data sets (Fig. 1). The number of case-control pairs was as follows: 9 sets for 1:1, 22 sets for 1:2, 74 sets for 1:3, 19 sets for 1:4, 5 sets for 1:5, 1 set for 1:6, and 3 sets for 1:7. Since no controls were still living for some cases especially elderly cases, there were a few sets in which the number of controls was less than three.

The interviews for cases were conducted with bereaved families between 2002 and 2015. Since most of those families were going through the process of compensation for mesothelioma related asbestos exposures due to the AC plant, they had sufficient information regarding their cases. On the other hand, most families of the controls did not have as much detailed information as did the bereaved families of mesothelioma death cases. For these reasons, the interviews for controls were conducted with the subjects themselves and their families, using the same questionnaire as for the cases, and by well-trained nurses with expertise in asbestos-related health hazards, who had been originally employed by Amagasaki City government for municipal surveillance and subsequently employed by the study group between 2015 and 2017.

The questionnaire consisted of more than 40 items, similar to those used for the Ministry of Environment’s survey regarding mesothelioma deaths due to environmental asbestos exposure. The questionnaire, which was performed by either a structured visit or a telephone interview, consisted of the following sections on the relationship of respondent with the index subject (cases and controls themselves): demographic characteristics including smoking history; status of occupational compensation certification; lifetime occupational history (date of entry/exit, employer's name, address, occupational category, job description, and handling of asbestos products); residential history (date of entry/exit, and address) during the period 1957–1975; crocidolite, which is considered to be the most toxic type of asbestos and is associated with the highest mesothelioma risk [4], was definitely allowed to be used in the plant [11, 15, 16]; and other possible environmental asbestos exposures such as domestic (cohabitants who washed clothes at home or brought work materials home, handled asbestos products, or worked at places with walls or ceilings sprayed with asbestos) or household (any exposure to asbestos-containing materials in the home) exposure. Environmental (non-occupational) exposure is generally divided into three sources according to the exposure pathway: neighborhood, domestic, or household [3]. In our study, neighborhood exposure that resulted from living near an emission point of airborne asbestos fibers was estimated from individual residential histories. Domestic exposure was estimated in relation to cohabitants occupationally exposed to asbestos in the same house, and household exposure was estimated as it related to any exposure to asbestos-containing materials in the home, such as fire-proof sheets and asbestos-sprayed walls and ceilings. Because individuals were considered to have multiple exposure sources, we intended to evaluate four types of exposure independently, according to relevant rating procedures: occupational, domestic, household, and neighborhood.

Collected occupational histories included "company name", "address", "employment period", "job description", and "the experience of direct asbestos handling", which was obtained as dichotomous data (Yes or No), using a check list of asbestos-related products, and if any of these applied to the subject, we determined the subject to be a direct handler. Basically, interviews were supposed to be in an open-question manner, except when a dichotomous answer was required. The following questions related to occupational exposures were required answers as dichotomous data: direct handling, and working at a place with sprayed asbestos walls or ceilings.

In order to control confounding effects due to occupational exposure, when evaluating the effects of non-occupational exposure, we excluded "Definite" exposure (subjects who responded "Yes" to "the experience of direct asbestos handling through their lifetime"). Since evaluating the effects of occupational exposure was not the aim of this study, we did not try to quantitatively evaluate the cumulative dose of asbestos exposure for these subjects. As a result, we excluded 32 cases and 61 controls, for a remaining total of 101 cases and 342 controls. Occupational exposure was then categorized into three tiers: "Convincing", "Possible", and "None", which were evaluated for probability of occupational exposure based on the individual's occupational history obtained from interviews. Three raters, who had been judges for asbestos-related occupational compensations, assigned each obtained case and control to one of three occupational exposures probability categories, referring to publicly available materials provided by the Ministry of Health, Labor and Welfare, and to a list of industries that included 176 or more work places, in which many employees were certified as occupational compensations in Amagasaki City. To gain expert consensus, we took the following steps: 1) each expert assigned the probability of occupational exposure in two rounds, 2) a summary including demographics was provided to all the experts with the reasons of judgement, 3) the experts were encouraged to revise their earlier assignments in light of the other members' comments, and 4) the final assignments were determined by a panel including three raters and all authors of the study.

We defined domestic exposure as exposure to asbestos fibers brought home by workers (who handled asbestos products or worked at places with walls or ceilings sprayed with asbestos) on their clothing or in their hair, or through living in the same house with occupationally-exposed individuals (who washed their clothes at home or brought home work materials), and coded it as either Yes or None in the dichotomous category.

We defined household exposure as exposure to asbestos-containing materials used in home structures (e.g., roofs, walls, insulation) or home improvement products, exposure to asbestos-sprayed walls at school, or exposure by playing at an asbestos factory, playing in the backyard of an asbestos factory, or playing with asbestos products. If any of the list of asbestos products applied to the subject, we coded it as Yes in the dichotomous category (None/Yes).

To evaluate for neighborhood asbestos exposure due to a large-scale AC plant, we used cumulative indices corresponding to the individuals' residential histories during an exposure period from 1957 to 1975, which was established by consensus among experts as the period when a large amount of crocidolite, called "blue asbestos", was used in the city and was considered the most toxic type of asbestos in relation to malignant mesothelioma. Based on this background, municipal surveillance, called the Epidemiological Analysis Survey of Asbestos Exposure, was conducted with the environmental exposure period set to 1957–1975. Focusing on airborne asbestos fibers derived from the AC plant, the relative concentration (unit, $1/m^3$) in each 100 m x 100 m grid was estimated, using a diffusion equation that considered meteorological conditions. The method assumed that an emission point of airborne asbestos was at the center of the premises of the plant and followed the diffusion equations as previously described in detail [11, 16]. Figure 2 depicts the distribution of geographically simulated relative asbestos concentrations across Amagasaki City, which were downscaled into a 10 m x 10 m grid by using spline interpolation. The contour lines show isolines of relative asbestos concentration, ranging from 1 to 10^7 (unit, $1/m^3$), and the color-coded concentric circles indicate crow-fly distances from the center of the plant premises.

By using residential histories based on the interviews and the Basic Resident Records in Amagasaki City, we obtained the geographic coordinate for each residential record. Geocoding with the Mapple Address Matching Tool (Shobunsya Inc.) was performed to convert the address of each residence into a geographic coordinate, a longitude and latitude pair, which represented a point on the city block called "Gaiku" (61.3% for cases and 79.9% for controls) or in the neighborhood called "Choh-aza" (38.7% for cases and 20.1% for controls). When the geocoding of old address names failed, we referred to detailed city maps to manually convert the old address into the current one. Based on the geographic coordinate, each residence was linked to the simulated relative asbestos concentration, as mentioned above.

We obtained residence-specific asbestos exposure calculated by the simulated relative concentration of airborne asbestos fibers multiplied by the duration at each residence (Table 3). Finally, we calculated the cumulative indices of neighborhood exposures by summing up the residence-specific exposures (unit, year/m^3) for each individual subject, taking into account the residential histories between 1957 and 1975 in Amagasaki City.

Conditional logistic regression analysis was employed to compute odds ratios (OR) and 95% confidential intervals (95% CI) in relationship to the neighborhood asbestos exposure (quintiles of the cumulative dose of neighborhood asbestos exposure in all controls), using STATA software (version 14.2/MP; Stata Corp., College Station, TX, USA). Additionally, the other covariates for adjustment were assessed for three tiers of occupational exposure and dichotomous variables for both domestic and household exposures. We defined tests with $P < 0.05$ as statistically significant.

Results

Demographics between the 133 cases and matched 403 controls were well-balanced (Table 1). It was expected that the distribution of respondents would be different between cases and controls, as the interviews for cases conducted by the government were conducted mainly with bereaved families but also with subjects if they were alive, while the interviews for controls were with the subjects and their families. We did observe some significantly different distributions between cases and controls ($P < 0.001$). The highest proportion of respondents in the male cases was “Spouse” (65.5%), followed by “Child” (22.6%) and “Subject” (7.1%), and in the male controls, the highest proportion of respondents was “Subject” (69.8%), followed by “Spouse” (16.4%) and “Child” (13.0%). The highest proportion of respondents in the female cases was “Child” (73.5%), followed by “Spouse” (20.4%) and “Subject” (4.1%), and in the female controls the highest proportion was “Subject” (51.8%), followed by “Child” (29.8%) and “Spouse” (13.5%).

We also observed that the distribution of “Definite” or “Non-definite” exposure in relation to occupational histories differed slightly ($P = 0.004$, Fisher’s exact test) between the cases and the controls in females.

After exclusion of 32 cases and 61 controls, considered as “Definite” exposure, we determined the distributions of all “Non-definite” exposures (101 cases and 342 controls) in relation to the exposure variable and the number of residences (Table 2). Statistically significant differences in occupational exposures were observed between cases and controls both in males and females ($P < 0.001$), despite no differences in the other exposures except for neighborhood exposure. To evaluate the distribution related to neighborhood exposure, we examined the number of residences per person in Amagasaki City during the period 1957–1975, and found no differences between cases and controls both in males and females (Table 2).

By using the cumulative indices corresponding to individuals’ residential histories, we evaluated the characteristics of all residential records (Table 3). Although there was no significant difference in the living duration at each single residence, there were statistically significant differences in the simulated relative asbestos concentrations between cases and controls ($P < 0.001$; Fisher's exact test). Moreover, statistical variances both in the simulated relative asbestos concentration per residence and in the residence-specific exposure per residence (multiplied by the living duration at each residence) were significantly different between cases and controls, with a median of 16.8 y/m^3 and 5.1 y/m^3, respectively ($P < 0.001$; Wilcoxon's rank sum test). This indicated that the highest proportion of residence-specific exposure was in the over 40 y/m^3 category for cases, in contrast to the less than 4 y/m^3 category for controls. Regarding distributions of the distance from the AC plant, most residents for the controls (67.8%) and less than half for the cases (41.7%) had lived in an area over 2 km from the center of the AC plant, with median distance of 2880.5 m and 1645.1 m, respectively, which was a statistically significant difference ($P < 0.001$; Wilcoxon's rank sum test).

The ORs for mesothelioma deaths in relation to neighborhood asbestos exposure were estimated by conditional logistic regression analyses, adequately adjusted for occupational, domestic, and household exposures both for males and females (Table 4). Neighborhood asbestos exposure was evaluated using the cumulative index, which was calculated by summing up residence-specific exposures (unit, year/m^3) in each individual subject. We calculated five quantiles of the cumulative dose of residence-specific exposures for all controls, and categorized them as Level 1, 2, 3, 4 or 5 in order from the lowest quintile. The distributions were then shown in each quintile level of neighborhood exposure for cases and controls, with values of the cumulative dose of neighborhood exposures at the border of each quintile. In reference to Level 1, ORs for Level 5 were 23.7 (95% CI: 3.8–147.2) for males and 26.0 (95% CI: 2.8–237.5) for females, and demonstrated a statistically significant increasing trend (P for trend < 0.001) related to the levels of neighborhood exposure, both in males and females.

Although not shown in Table 4, we also estimated the following ORs for combined males and females: 21.4 (95% CI: 5.8–79.2) for Level 5 in neighborhood exposure, 25.4 (95% CI: 7.1–90.3) for 'Convincing' in occupational exposure, 4.4 (95% CI: 0.3–57.6) for domestic exposure, and 2.0 (95% CI: 0.7–5.7) for household exposure.

In addition, to evaluate which had a larger impact on the assessment for risk of mesothelioma deaths, asbestos concentration related to distance from the AC plant or duration of living was compared with the cumulative indices, based on a representative residence for each individual subject, which addressed the maximum (highest) value of the residence-specific exposure or the distance at the nearest residence from the AC plant for a year or more (Supplementary Table). Approximately 90% of both cases and controls in Level 5 were re-classified as Level 5, even though they were based on the maximum residence-specific exposure only. Also in Level 4, 80% or more of both cases and controls were re-classified as Level 4. These findings suggested that maximum residence-specific exposure might be a useful indicator in relation to neighborhood exposure. However, neither the simulated relative concentrations nor the durations based on the representative residence showed substantial differences between cases and controls. Furthermore, the distribution of distance from the AC plant based on the nearest residence did not show any differences between cases and controls. We also observed that 26.5% of cases and 22.1%

of controls had been living in areas less than 500 m from the plant, compared to 4.1% of cases and 2.9% of controls who had been living in areas 2 km or more from the plant.

Discussion

A strength of this study was its nested case-control design, which provided essential information including all residential histories and outcomes such as death/alive/moveout, in a fixed population. The Amagasaki City long-term resident cohort enabled us to utilize the nested case-control design to elucidate an increased risk of mesothelioma death quantitatively associated with neighborhood exposure, as well as occupational exposure, by controlling for other relevant asbestos exposures, and by properly adjusting for considerable confounding factors.

In our previous studies, SMRs associated with neighborhood exposure showed a substantial gender difference, with values of 6.75 for males and 14.99 for females [13], which were thought to be due to an effect of occupational exposure included in the national mortality rates used as a reference. In our previous study (Kurumatani and Kumagai, 2008), SMRs were estimated by excluding mesothelioma cases that had possible occupational exposure from the numerator only and not excluding occupational exposure from the denominator. As a result, SMRs were 2.6 for males and 9.9 for females, demonstrating a much greater difference. Such gender differences were variable, depending on the attributable proportion of occupational exposure. Thus, we thought that a nested case-control design would allow us to obtain essential information related to the neighborhood exposure, which depends on individual residential histories, and to combine the Basic Resident Records with interview data from the surveillance on mesothelioma deaths, including individuals' occupational histories and other histories related to asbestos exposures. The results showed that adjusted ORs in the top quintile were 21.4 for all subjects, 23.7 for males, and 26.0 for females, compared to the bottom quintile. Our findings might be the first to demonstrate no gender difference in the risk of mesothelioma death associated with neighborhood exposure due to a large-scale AC plant in Asia.

A recent pooled analysis of 21 AC worker cohorts in Italy [17] showed a similar tendency in relation to gender difference, with significant increases in mortality from all causes (SMR: men 1.2; women 1.3) and from asbestos-related diseases such as malignant neoplasm of the peritoneum (SMR: men 14.2; women 15.1) and the lung (SMR: men 1.7; women 1.7), except for pleura (SMR: 22.4 and 48.1, respectively). That study also showed that the rate ratio (RR) by Poisson regression analyses for pleural and peritoneal malignant neoplasms increased with cumulative exposure (fiber-type weighted index), while with the time since first exposure it showed an increase in the first four decades, followed by a plateau in both genders for pleural malignant neoplasm. A population-based case-control study in France [18] demonstrated that ORs for the highest occupational exposure were 13.2 for males and 18.2 for females compared to those never exposed, also indicating no substantial gender differences. Regarding the association with non-occupational exposure, ORs for the highest probability of exposure were 4.6 for males and 7.5 for females compared to those never exposed. Furthermore, the population attributable risk (ARp) for those non-occupational subjects was 20.0% in males and 38.7% in females, which suggests that the overall population-attributable risk of asbestos exposure in females was largely driven by non-occupational exposure, considering the difficulty in assessing domestic or environmental exposure.

Regarding occupational exposure, we employed two evaluation steps: the first step was exclusion of the direct asbestos exposure from analyses, and 32 cases and 61 controls were consequently excluded; the second step was classification according to reliability of occupational exposures. We know the magnitude of the impact of occupational exposure is extremely large, compared to the other asbestos-related exposures, and it is difficult to control the effects properly. We excluded direct exposure, defined as “Definite”, because it was the most efficient way to control its effects, as the primary aim was to evaluate the effect of non-occupational exposure. Then, we classified the study population into “None”, “Possible”, and “Convincing” based on reliability to make subjects eligible for evaluation by exposure intensity. Although ORs for occupational exposure were relatively high in the multivariate analysis, especially for males, compared to those for other non-occupational exposure, this should be interpreted with caution, as they could be either overestimated or underestimated.

Although few studies of neighborhood exposure have been reported, and there is large heterogeneity among results from those studies [19], a recent meta-analysis reported an increased risk of mesothelioma death by exposure types, with a summary relative risk estimate (SRRE) of 5.33 (95% CI: 2.53–11.23) from neighborhood exposure, 4.31 (95% CI: 2.58–7.20) from domestic exposure, and 2.41 (95% CI: 1.30–4.48) from household exposure [7]. Other researchers reported a clear increasing trend in relationship to the cumulative exposure index, demonstrating that the highest OR was 23.3 (95% CI: 2.9 -186.9), but they did not assess the exclusive estimates that could be associated with neighborhood, domestic, and household exposures [20]. Magnani and colleagues conducted a case-control study in Casale, Italy, and found a significantly increased risk of mesothelioma in the population that had lived in the city, with an OR of 20.6 (95% CI: 6.2–68.6) [21]. In the same city, another study estimated OR in relationship to distance from an AC plant, however, the results were thought to be due to combined exposure of the neighborhood and household [22]. In a study that looked at distance from an AC plant in Bari, Italy, the highest OR (5.29 [95% CI: 1.18–23.73]) was for people living within a range up to 500 m from the center of the plant [23]. A population-based case-control study conducted in six areas in Italy, Spain, and Switzerland estimated that the OR for high probability of environmental exposure (living within 2000 m of asbestos mines, AC plants, asbestos textiles, shipyards, or brakes factories) was 11.5 (95% CI: 3.5–38.2), while the OR for moderate or high probability of domestic exposure was 4.81 (95% CI: 1.8–13.1) [6]. Most classifications regarding non-occupational exposures described in the current literature were considerably heterogeneous. For example, different or combined definitions of environmental asbestos exposure have been used in various published studies [24]. However, regardless of the different indicators and range of categories in those studies, the risk magnitudes by internal comparisons, indicated as ORs or RRs, seem consistent with our findings.

For the second evaluation step, we employed cumulative indices to assess neighborhood asbestos exposure using the population-based residence records. That process contributed to our quantitative risk assessment for neighborhood exposure by calculating the cumulative dose of exposures for each individual subject, taking into account both duration and concentration of the exposure. Resulting ORs for

Level 5 were 23.7 (95% CI: 3.8–147.2) for males and 26.0 (95% CI: 2.8–237.5) for females in reference to Level 1, with an increasing trend (P for trend < 0.001). Thus, our results demonstrated that the risk of the neighborhood exposure associated with mesothelioma deaths due to the AC plant in Amagasaki City increased in a dose-dependent manner, and there were no gender differences in the magnitude of risk. We suggest that for 90% of the high-risk population, the assessment for neighborhood exposure might be possible by single residence data that corresponds to the maximum exposure.

There are some limitations in the study. First, we observed differences between cases and controls in the type of respondents. The highest proportion of respondents among controls was subjects, while the highest proportion of respondents among cases was a spouse or a child. Case interviews were thought to contain critically important information for the Ministry of Environment to make decisions about compensation certification, hence, the bereaved families had detailed information about the cases' occupational histories and any other possibilities related to asbestos exposure at that time. In contrast, most families of controls, even though they were spouses and children, were not well informed about details of subjects' occupational and residential histories throughout their lifetime. We therefore needed to interview control subjects as well as their families to collect data with the same accuracy as that for the cases. For 342 controls which were used for the analysis regarding neighborhood exposure, we observed the distribution of occupational exposure: no-occupational exposure 159 (78%), possible occupational exposure 33 (16%) and convincing occupational exposure 12 (6%) when subjects responded, while no-occupational exposure 90 (65%), possible occupational exposure 39 (28%) and convincing occupational exposure 9 (7%) when non-subjects responded. Since the difference was not substantial among different types of respondents, we believe the impact would be minimal.

Second, since participation rates were different between cases and controls, this needs consideration. Out of 379 mesothelioma cases, we obtained contact information for 269 (71.0%) cases, of which 167 (62.1%) cases completed interviews, resulting in a 44.1% total participation rate. On the other hand, of 5,320 control candidates, we obtained contact information for 4,191 (78.8%) candidates, of which 403 (9.6%) controls completed interviews, resulting in a 7.6% total participation rate. Therefore, higher cooperation with survey interviews was observed for cases than for controls, while the proportion of contact information availability was almost the same between cases and controls. Case candidates who did not cooperate had reasons such as: 1) unwilling to look back on the past, 2) not well informed about history of the indexed subject, or 3) already recognized through industrial compensation. On the other hand, we could not collect any information for the reasons control candidates did not participate in the interviews.

A third limitation was that we obtained the list of mesothelioma deaths from Japanese vital statistics, which began to record the primary cause of death according to ICD-10 in 1995, and the cause of death was posted from a death certificate, without histological verification. A national survey of malignant mesothelioma and asbestos exposure between 2003 and 2008 confirmed that 929 diagnoses in 1,111 cases extracted from the National Vital Statistics that used the code C45 with informed consent and medical information were confirmed as exact mesothelioma deaths with histological subtypes (83.6%), 101 diagnoses were suspected mesothelioma deaths (9.1%), and 81 diagnoses were lung cancers (5.2%) [14]. Since the Kubota Shock in 2005, we thought that the diagnosis of mesothelioma might be more accurate than the previous estimate.

A fourth limitation was that we did not consider the period 1975–1995 when the AC plant continued to use asbestos (not crocidolite) as an exposed period. The aim of the study was to elucidate a quantitative assessment for mesothelioma deaths with neighborhood exposure due to a large-scale AC factory. To extend the exposure period to include 1975–1995, we would have to use two or more different weights for a 1-year exposure for 1957–1975 and 1975–1995, because the carcinogenic effect of crocidolite and other types of asbestos differs substantially. This would result in quantitative assessments that are more complex and difficult to interpret. Therefore, we thought that limiting the exposure period to 1957–1975 would be an appropriate way to make the findings easy to understand. Additionally, we did not consider asbestos fibers that had fallen on the ground and remained there after emission in the evaluation for neighborhood exposures.

The final limitation is that simulated asbestos concentrations were determined from several assumptions and the unit was based on a 10 m x 10 m grid resolution. Regarding the covariates, it might be necessary to consider all specific exposures in daily living, such as walking to school, gardening, and working in agricultural.

A recent world-wide trend assessment for excess risk of mesothelioma deaths used a period analysis from 1996 to 2005 to demonstrate a significant annual increased rate in Japan of 3.9%, with overall quite large disparities between countries [25]. Similarly, our previous studies in Amagasaki City demonstrated that mesothelioma deaths increased significantly in long-term resident cohorts both in males and females from 2002 to 2015, with consistent trends in the three periods of 2002–2006, 2007–2011, and 2012–2015. A recent paper suggested that non-occupational exposure mainly contributed to the overall population-attributable risk, especially for females [18]. Although it was only a municipal administrative report in Amagasaki City, a gradual increase in mesothelioma deaths from non-occupational exposures was observed for males (19% during 2002–2007, 35% during 2008–2015) and females (39% during 2002–2007, 73% during 2008–2015). One possible consideration might be an age-cohort effect, in which the risk of mesothelioma remains and never diminishes for the people who were exposed in early life, even after removal of the AC plant [26]. Therefore, we should continue to pay close attention to trends in the risk of mesothelioma death associated with low-dose asbestos exposures including neighborhood exposure.

Conclusions

We demonstrated a dose-dependent increase in mesothelioma death associated with neighborhood asbestos exposure due to a large-scale AC plant in Japan by using cumulated neighborhood asbestos exposure and adjusting properly for occupational and other asbestos exposures. Our findings suggest that the risk of mesothelioma death with neighborhood exposure persists and will not be diminished for many years, even though it has been decades since the AC plant closed.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Osaka University Hospital (authorization: no.15100, August 13th, 2015).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed for the present study are not openly available due to reasons of sensitivity about the affected residents' data, but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YK: Design of the study, conduct of this project, administration of data analysis, writing original draft, review, and editing. LZ: Data management and analysis, and construction of tables. RL: Data collection and coordination of the interviews. MS and NK: Conceptualizing and supervising the study, and critical revision of the article. TN: Geographical mapping of the relative asbestos concentrations, assessment of the neighborhood exposures and critical revision of the article. SK: Simulating the relative asbestos concentrations, supervising the assessment of occupational exposures, and critical revision of the article. JG: Coordination of the investigation and administration of the resources in Amagasaki City. TS: Principal investigator of the study, overview and critical revision of the article. All authors read and approved the final manuscript.

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References

1. Wagner JC, Sleggs CA, Marchand P: **Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province**. Br J Ind Med 1960, **17**:260–271.
2. Albin M, Magnani C, Krstev S, Rapiti E, Shefer I: **Asbestos and cancer: An overview of current trends in Europe**. Environ Health Perspect 1999, **107 Suppl 2**:289–298.
3. Howel D, Arblaster L, Swinburne L, Schweiger M, Renvoize E, Hatton P: **Routes of asbestos exposure and the development of mesothelioma in an English region**. Occup Environ Med 1997, **54**(6):403–409.
4. Hansen J, de Klerk NH, Musk AW, Hobbs MS: **Environmental exposure to crocidolite and mesothelioma: exposure-response relationships**. Am J Respir Crit Care Med 1998, **157**(1):69–75.
5. Magnani C, Borgo G, Betta GP, Botta M, Ivaldi C, Mollo F, Scelzi M, Terracini B: **Mesothelioma and non-occupational environmental exposure to asbestos**. Lancet 1991, **338**(8758):50.
6. Magnani C, Agudo A, Gonzalez CA, Andrion A, Calleja A, Chellini E, Dalmasso P, Escolar A, Hernandez S, Ivaldi C *et al*: **Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos**. Br J Cancer 2000, **83**(1):104–111.
7. Xu R, Barg FK, Emmett EA, Wiebe DJ, Hwang WT: **Association between mesothelioma and non-occupational asbestos exposure: systematic review and meta-analysis**. Environ Health 2018, **17**(1):90.
8. Oshima H: **Five cases with mesothelioma living near a now-defunct asbestos cement plant in Amagasaki City** (**in Japan**). In: *Mainichi Newspaper.* 2005.
9. Kubota-Corporation: **Demographic data of employees with asbestos-related diseases in Kanzaki Plant**, **a now-defunct asbestos cement plant in Amagasaki City**, **Hyogo** (**in Japan**). 2005.
10. Amagasaki-city: **A report on the amount of asbestos used in the past by 136 companies in Amagasaki City**, **Hyogo** (**in Japan**). In.; 2006.
11. Kurumatani N, Kumagai S: **Mapping the risk of mesothelioma due to neighborhood asbestos exposure**. Am J Respir Crit Care Med 2008, **178**(6):624–629.
12. Nakaya T: **Malignant mesothelioma** (**ICD10**:**C45**). In: *Time Bomb In The Atlas of Health Inequalities in Japan.* Edited by Nakaya TaIY: Springer Nature; 2019: 121–126.
13. Zha L, Kitamura Y, Kitamura T, Liu R, Shima M, Kurumatani N, Nakaya T, Goji J, Sobue T: **Population-based cohort study on health effects of asbestos exposure in Japan**. Cancer Sci 2019, **110**(3):1076–1084.
14. Gemba K, Fujimoto N, Kato K, Aoe K, Takeshima Y, Inai K, Kishimoto T: **National survey of malignant mesothelioma and asbestos exposure in Japan**. Cancer Sci 2012, **103**(3):483–490.

15. Kurumatani NK, S.: **Mesothelioma Due to Neighborhood Asbestos Exposure**: **A Large-Scale**, **Ongoing Disaster Among Residents Living Near a Former Kubota Plant in Amagasaki**, **Japan**. In: *Asbestos Disaster: Lessons from Japan's Experience.* Edited by Kenichi Miyamoto KM, Hiroyuki Mori. Japan: Springer; 2011: 75.
16. Kumagai S, Kurumatani N: **Asbestos fiber concentration in the area surrounding a former asbestos cement plant and excess mesothelioma deaths in residents**. Am J Ind Med 2009, **52**(10):790–798.
17. Luberto F, Ferrante D, Silvestri S, Angelini A, Cuccaro F, Nannavecchia AM, Oddone E, Vicentini M, Barone-Adesi F, Cena T *et al*: **Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy**. Environ Health 2019, **18**(1):71.
18. Lacourt A, Gramond C, Rolland P, Ducamp S, Audignon S, Astoul P, Chamming's S, Gilg Soit Ilg A, Rinaldo M, Raherison C *et al*: **Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma**. Thorax 2014, **69**(6):532–539.
19. Bianchi C, Bianchi T: **Malignant mesothelioma in Eastern Asia**. Asian Pac J Cancer Prev 2012, **13**(10):4849–4853.
20. Ferrante D, Mirabelli D, Tunesi S, Terracini B, Magnani C: **Pleural mesothelioma and occupational and non-occupational asbestos exposure: a case-control study with quantitative risk assessment**. Occup Environ Med 2016, **73**(3):147–153.
21. Magnani C, Dalmasso P, Biggeri A, Ivaldi C, Mirabelli D, Terracini B: **Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: a case-control study in Casale Monferrato, Italy**. Environ Health Perspect 2001, **109**(9):915–919.
22. Maule MM, Magnani C, Dalmasso P, Mirabelli D, Merletti F, Biggeri A: **Modeling mesothelioma risk associated with environmental asbestos exposure**. Environ Health Perspect 2007, **115**(7):1066–1071.
23. Musti M, Pollice A, Cavone D, Dragonieri S, Bilancia M: **The relationship between malignant mesothelioma and an asbestos cement plant environmental risk: a spatial case-control study in the city of Bari (Italy)**. Int Arch Occup Environ Health 2009, **82**(4):489–497.
24. Liu B, van Gerwen M, Bonassi S, Taioli E, International Association for the Study of Lung Cancer Mesothelioma Task F: **Epidemiology of Environmental Exposure and Malignant Mesothelioma**. J Thorac Oncol 2017, **12**(7):1031–1045.
25. Nishikawa K, Takahashi K, Karjalainen A, Wen CP, Furuya S, Hoshuyama T, Todoroki M, Kiyomoto Y, Wilson D, Higashi T *et al*: **Recent mortality from pleural mesothelioma, historical patterns of asbestos use, and adoption of bans: a global assessment**. Environ Health Perspect 2008, **116**(12):1675–1680.
26. Myojin Tomoya AK, Okumura Jiro, Uchiyama Iwao: **Future Trends of Mesothelioma Mortality in Japan Based on a Risk Function**. Industrial Health 2012, **50**:197–204.

Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

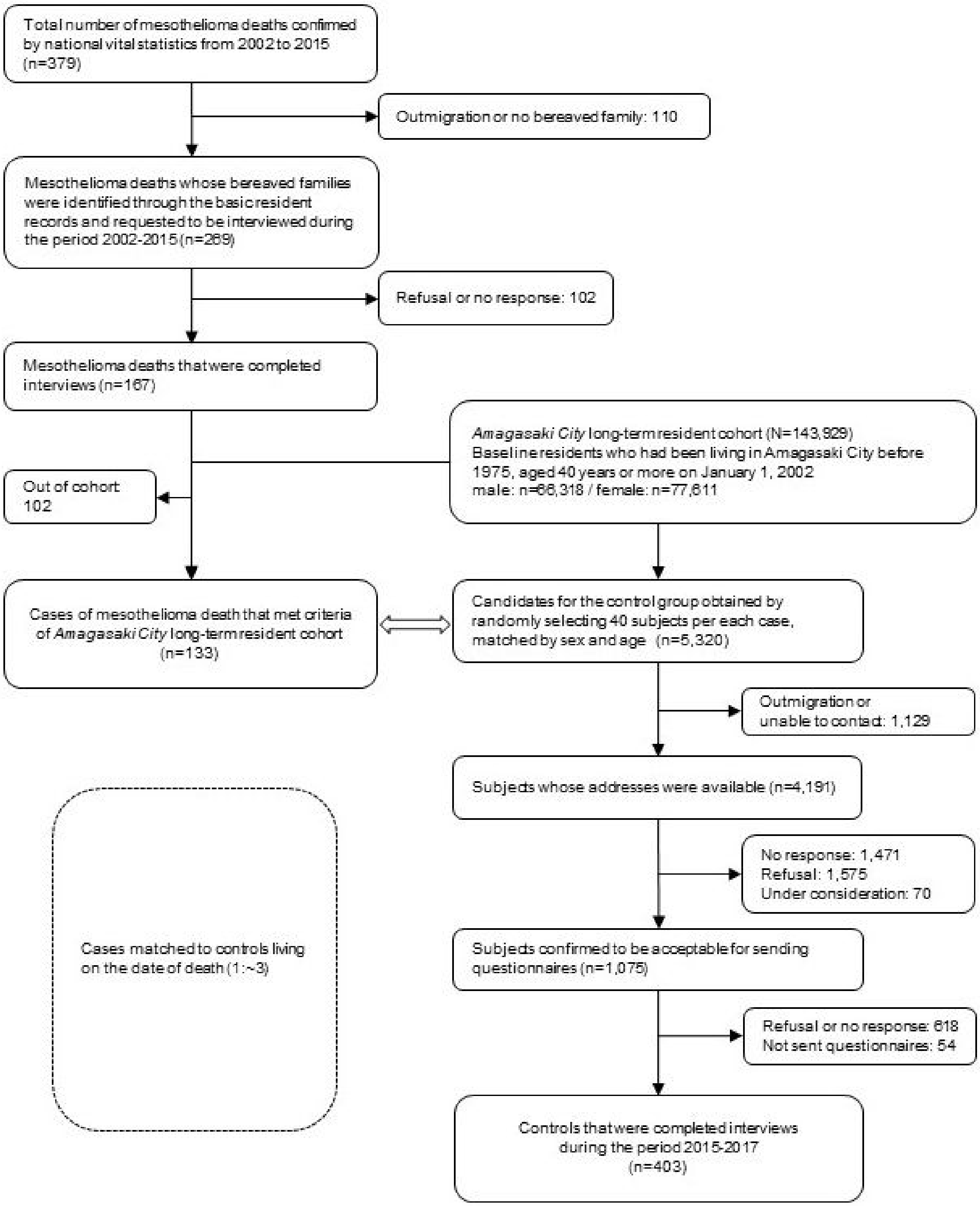

Figure 1

Flow diagram of study population enrollment in the Amagasaki City long-term resident cohort; cases and matched controls.

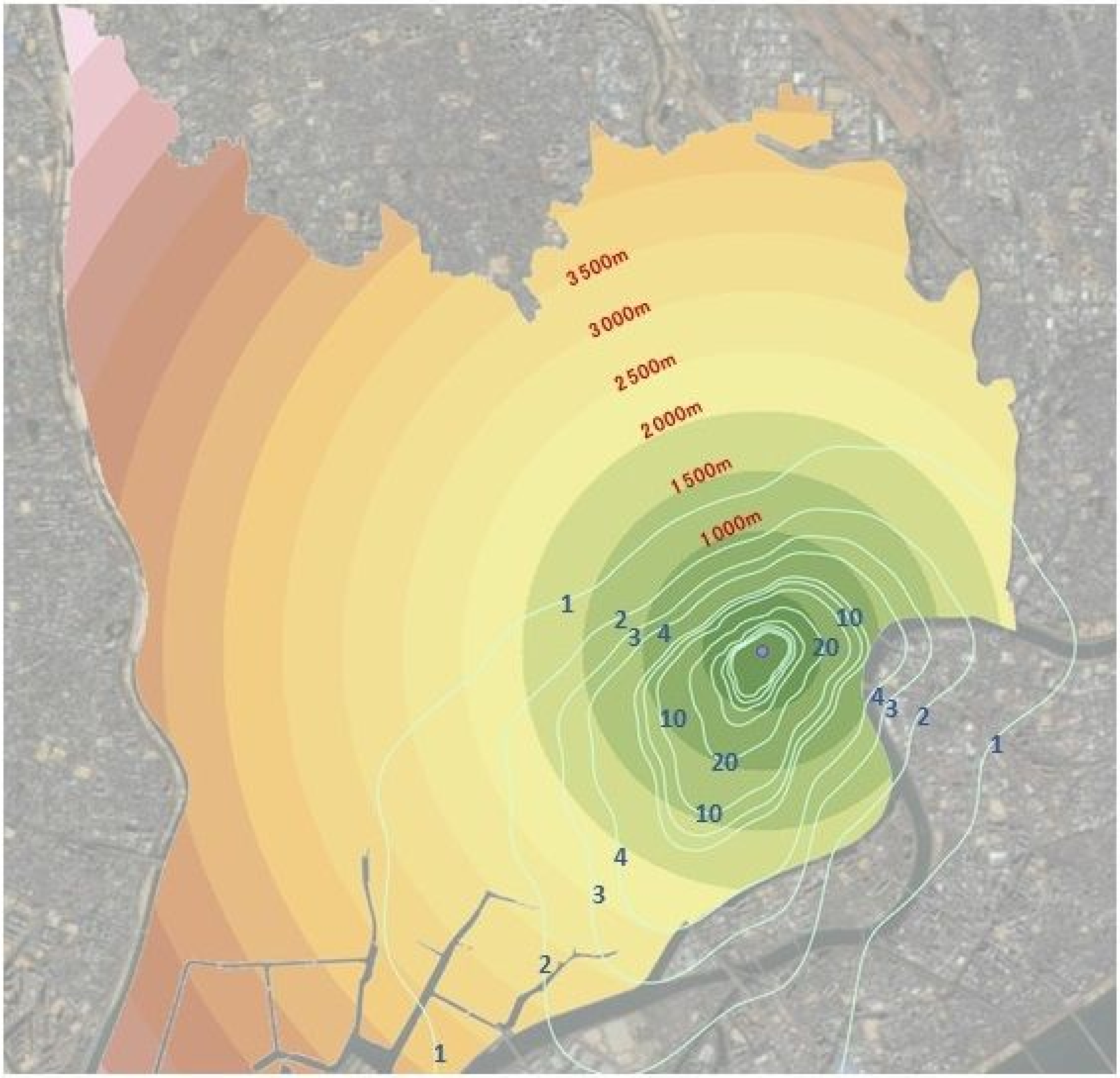

Figure 2

Distribution of geographically simulated relative asbestos concentrations accounting for meteorological conditions overlaid on Amagasaki City.

The blue number depicts the simulated relative asbestos concentration [unit: m^{-3}].

The red number depicts the straight line distance from the center of the AC plant premises.

Supplementary Files

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- AmagaskiNCCstudysupplemenrtarytable.xlsx
- AmagaskiNCCstudyTable1amended.xlsx
- AmagaskiNCCstudyTable2amended.xlsx

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- AmagaskiNCCstudyTable4amended.xlsx