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

This was 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 to 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.

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.

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.

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, 2], and few studies have shown

whether the environmental exposures, including neighborhood, domestic, and household exposure, would quantitatively elevate the risk of mesothelioma death [3–5]. In Amagasaki City on 27 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 [6]. From 1957 to 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 [7, 8]. By using spatial epidemiological mapping at the municipality level across Japan, researchers revealed distinctive geographical concentrations of elevated risk of mesothelioma death in several cities including Amagasaki City, especially in women during the latest observation period between 2010 and 2014 [9].

In our previous study, we showed that standardized mortality ratios (SMRs) for malignant mesothelioma compared to nation-wide mesothelioma mortalities were 6.75 for males and 14.99 for females in Japan between 2002 and 2015 [10]. Previously, remarkable increases in SMRs had been demonstrated for malignant mesothelioma in a clearly dose-dependent manner that were associated with simulated relative concentrations of airborne asbestos due to an AC plant [11]. However, SMRs in that study, especially in male subjects, were considered to be underestimated because they excluded all asbestos-related workers from the population eligible for analyses. In general, an effect size of occupational exposure is quite large compared to non-occupational exposures, including neighborhood exposure, so studies should carefully consider ways to control for the effect of occupational exposure as a confounder, and one way is to use a case-control study design for proper adjustment. The aim of this study was to elucidate the quantitative association between neighborhood exposure and mesothelioma deaths due to a large-scale AC plant (Kubota Kanzaki Factory) in Amagasaki City by more efficiently controlling for occupational exposure.

Methods

We conducted a population-based nested case-control study in Amagasaki City. The study population, who had continuously been living in the city before 1975 and at least until the beginning of 2002, were fixed as the Amagasaki City long-term resident cohort, and were followed up from 1 January 2002 to 31 December 2015 for death and outmigration status using the Basic Resident Records. The cohort consisted of 143,929 residents aged 40 years or more at baseline, as described in our previous study [10]. A flow diagram of the study is depicted in Fig. 1.

Since 2010, the Amagasaki City Government has been conducting interviews with bereaved families of those who died of mesothelioma, based on the list of mesothelioma deaths provided by vital statistics. In municipal administrative reports, a total of 379 mesothelioma deaths were recorded during the period between 2002 and 2015, however, 110 of these diseases were not identified through the Basic Resident Records due to outmigration or absence of bereaved family. Furthermore, of the 269 identified mesothelioma deaths, 102 bereaved families refused to be interviewed or could not be contacted. Of the

167 mesothelioma deaths (62.1%) for which bereaved families accepted to be interviewed, 133 mesothelioma deaths met inclusion criteria of the Amagasaki City long-term resident cohort and were thus defined as the cases in our study (Fig. 1).

Controls were selected from the Amagasaki City long-term resident cohort, were matched individually to each case by sex and age (birth date $\pm$ 12 months), and were alive on the exact date of death of their corresponding cases. In order to obtain three controls per case to have a 1:40 case-control ratio, we randomly selected 5,320 residents for controls. Of these, addresses of 4,191 residents and their closest family members were confirmed through the Basic Resident Records and were eligible for assessment (Fig. 1). Letters for contact availability were sent to these 4,191 residents through the local government of Amagasaki City, and 2,720 residents (64.9%) responded. Of these 2,720 residents, 1,021 were eligible to receive postal questionnaires regarding approval for participation in the study. From these 1,021 eligible residents, consent was obtained for 403 residents (39.5%), who were consequently interviewed for the study. These 403 controls were matched to 133 cases. All interviews for the controls were completed between 2015 and 2017, using the same questionnaire that was applied for cases. Finally, the number of sets and ratios for matching were 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.

Well-trained nurses with expertise in asbestos-related health hazards conducted interviews of all individuals for both cases and controls between 2002 and 2017, using a standardized questionnaire. The questionnaire, which was conducted 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; residential history during the considerable asbestos exposure period of 1957–1975, when crocidolite was definitely used in the plant; and other possible environmental asbestos exposures such as domestic or household exposure. Environmental (non-occupational) exposure is generally divided into three sources according to the exposure pathway: neighborhood, domestic, or household. 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 separately, according to relevant rating procedures: occupational, domestic, household, and neighborhood.

We collected occupational histories, which included “company name”, “address”, “employment period”, “job description”, and “experience of handling directly any asbestos products (None/Yes)”. For the assessment of occupational exposure, a subject who had any self-reported experience of direct exposure was classified as “Definite” exposure (Table 1). For further assessment, the remaining subjects classified as “Non-definite” exposure were divided into three tiers: “Convincing”, “Possible”, and “None”, which were

evaluated for the probability of occupational exposure based on an individual's occupational history obtained from the interview. Three raters, who had many years of experience with judgement of asbestos-related occupational compensations, assigned probabilities to all the obtained data related to occupational exposure, referring to publicly available materials and relevant documents provided by the Ministry of Health, Labor and Welfare. 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 experts with reasons of judgements, 3) experts were encouraged to revise their earlier assignments in light of the other members' comments, and 4) the final assignment was determined by a reliable panel of experts. To confirm the "Definite" group for final analyses, we excluded 32 cases and 61 controls because they could have had a large effect on the relationship between neighborhood exposure and mesothelioma risk, which was the main interest of this study.

We defined domestic exposure as the exposure to asbestos fibers brought home by workers on their clothing or in their hairs or through living in the same house with occupationally-exposed individuals, and coded it as a dichotomous category (None/Yes) according to the corresponding questionnaires. We defined household exposure as having exposure to asbestos-containing materials used in home structures (e.g., roofs, insulation) or home improvement products. If there was at least one item in the list of considered asbestos-related products, we coded it as a dichotomous category (None/Yes) according to the corresponding questionnaires.

Focusing on airborne asbestos fibers derived from the AC plant, we estimated the relative asbestos concentration (unit, $1/\text{m}^3$) in each 100 m x 100 m grid, using diffusion equations and meteorological conditions at that time. 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, 12]. 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, $1/\text{m}^3$), and the color-coded concentric circles indicate crow-fly distances from the center of the premises of the plant. Residential histories in Amagasaki City during the exposure period of 1957–1975 were confirmed for each individual address and duration as precisely as possible based on the interview data and the Basic Resident Records. 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. By using the geographic coordinate, each residence was linked to the simulated relative asbestos concentration, as mentioned above. In order to evaluate the cumulated asbestos exposure, taking into account individual residential histories, we calculated the cumulative dose of neighborhood exposures by summing the residence-specific exposures (unit, year/m^3) obtained from the relative asbestos concentration (unit, $1/\text{m}^3$) multiplied by the duration (unit, year) (Table 3).

Odds ratios (ORs) in relationship to neighborhood exposure (quintiles of cumulative dose of asbestos exposure in the controls) were estimated separately for men and women by conditional logistic regression analysis, using the STATA software (version 14.2/MP; Stata Corp., College Station, TX, USA). Covariates for adjustment were assessed as 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 of the 133 cases and 403 matched controls were generally well-balanced, however, a few differences were observed (Table 1). For the matched controls, we interviewed both bereaved families and subjected persons, but the highest proportion of interviews was with subjected persons both for males (69.8%) and females (51.8%). In the male cases, the highest proportion of interviews was with the spouse (65.5%), while in the female cases, the highest proportion of interviews was with the child (73.5%). Regarding asbestos exposure, the number of subjects with definite occupational asbestos exposure who had directly experienced handling asbestos products was 26 (31.0%) for cases and 59 (22.5%) for controls in males, and 6 (12.2%) for cases and 2 (1.4%) for controls in females, with a slightly higher proportion among females ($P = 0.001$, Fisher's exact test) (Table 1).

After the exclusion of 32 cases and 61 controls with a history of directly handling asbestos products, Table 2 presents the demographic distribution of 101 cases and 342 controls with occupational, domestic, and household asbestos exposure. The proportion of cases that had convincing occupational exposure was 31.0% for males and 4.7% for females, which was much higher than that seen in controls (9.4% for males and 1.4% for females). The proportion of subjects with no occupational exposure was 82.7% for controls and 53.5% for cases in females, and 66.0% for controls and 37.9% for cases in males, which demonstrated that more than half of the cases were occupationally exposed to asbestos regardless of the intensity, especially in males. Overall for domestic and household asbestos exposures, we observed relatively higher proportions in the cases than in the controls.

No substantial differences in the number of residences per person were observed between cases and controls (Table 2). The characteristics of all residential records in the 101 cases and 342 controls during the potential exposure period of 1957–1975 are presented in Table 3. Although no substantial differences were observed in the duration lived at each single residence, statistically significant differences ($P < 0.001$; Fisher's exact test) between cases and controls were observed for the simulated relative asbestos concentrations. In addition, medians for both the simulated relative asbestos concentration and the residence-specific exposure (calculated by concentration multiplied by duration at each residence) showed statistically significant differences between cases and controls ($P < 0.001$; Wilcoxon's rank sum test). Moreover, the distribution of residence-specific exposure was significantly different between cases and controls, with the highest proportion observed in the lowest category in controls, and a broad distribution observed in cases. The median distance from the AC plant in the cases was lower than that in the controls, with a statistically significant difference ($P < 0.001$; Wilcoxon's rank sum test).

Table 4 presents ORs in reference to the lowest level (Level 1), according to quintile of neighborhood exposure in the controls, by using a conditional logistic regression analysis adjusted for occupational, domestic, and household exposures for males and females separately. The highest OR for Level 5 was 23.7 (95% CI: 3.8 to 147.2) in males and 26.0 (95% CI: 2.8 to 237.5) in females. Moreover, ORs increased remarkably as the exposure level became higher, with statistically significant trends (P for trend < 0.001) both in males and females. We also observed that nearly 50% of cases were classified as the highest level of neighborhood exposure (Level 5). In relationship to occupational exposure, the highest OR for the 'Convincing' category was 40.0 (95% CI: 7.3 to 219.7) in males and 6.9 (95% CI: 0.6 to 80.3) in females, with substantially higher associations in males compared to females. The OR for domestic exposure was 5.5 (95% CI: 0.4 to 93.4) in females. The OR for household exposure was 3.7 (95% CI: 1.0 to 14.4) in males and 0.7 (95% CI: 0.1 to 4.2) in females in reference to the no exposure groups, respectively. We also calculated ORs for combined males and females: the OR for highest level of neighborhood exposure (Level 5) was 21.4 (95% CI: 5.8 to 79.2), the OR for the 'Convincing' category of occupational exposure was 25.4 (95% CI: 7.1 to 90.3), the OR for domestic exposure was 4.4 (95% CI: 0.3 to 57.6), and the OR for household exposure was 2.0 (95% CI: 0.7 to 5.7).

Discussion

This was a population-based nested case-control study to evaluate the risk of mesothelioma death associated with neighborhood asbestos exposure due to a large-scale AC plant in Amagasaki, Japan. The results demonstrated that ORs in the top quintile were 21.4 for all, 23.7 for males, and 26.0 for females compared to the bottom quintile, suggesting that there were no substantial gender differences in relationship to the magnitude of risk.

In our previous studies, SMRs associated with neighborhood exposure showed a substantial sex difference because the effect of occupational exposure was higher in males than females and not controlled appropriately. We reported SMRs of 6.75 for males and 14.99 for females [10] because the effect of occupational exposure was included in the national mortality rates used as reference rates, which resulted in lower SMR for males than females. In the study by Kurumatani and Kumagai (2008), SMRs were estimated further by excluding mesothelioma cases that had possible occupational exposure from the numerator only and not excluding occupational exposure from the denominator. As a result, SMR was 2.6 for males and 9.9 for females, showing a much greater difference. Such sex differences were variable, depending on the attributable proportion of occupational exposure. Thus, we adopted a nested case-control design, by adequately taking into account the large effect of occupational asbestos exposure on the evaluation for neighborhood asbestos exposure, collecting enough data related to an individual's occupational and non-occupational exposure within the whole cohort population.

A recent pooled analysis of 21 AC worker cohorts in Italy [13] 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: 1.7 and 1.7), except for pleura (SMR: 22.4 and 48.1). It 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 [14] 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, suggesting 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.

In order to adjust properly for occupational exposure, we adopted two independent steps, an exclusion of direct occupational exposure and a rating for the reliability of exposure, and consequently 32 cases and 61 controls were excluded from our analyses. There was no doubt that the experience of directly handling asbestos products could have a significant impact on the evaluation for non-occupational exposure, however, it could not be used for proper assessment of occupational exposure due to lack of information on exposure intensity. The remaining cases and controls after exclusion were classified into three mutually exclusive tiers that were based on the reliability of exposure and contributed to adequate adjustments by using a conditional logistic regression model. We observed that the risk magnitude of occupational asbestos exposure was comparably higher than that of non-occupational exposure, demonstrating that ORs of “Convincing” compared to “None” were 25.4 for all, 40.0 for males, and 6.9 for females to suggest that the sex differences seemed to be fair.

To assess neighborhood exposure, we used cumulative indices of individuals’ residence-specific asbestos exposures, calculated by the relative concentration of airborne asbestos fibers multiplied by the duration at each residence during the potential exposure period (1957–1975). Many studies have evaluated neighborhood asbestos exposure by distance or by the simulated relative concentration of airborne asbestos fibers based on the nearest residence from the emission point. In order to clarify the effect of distance on the contribution to our cumulative indices, we chose only one residence, which addressed the maximum (highest) value of residence-specific exposure and compared characteristics of the cases and controls. Table 5 shows the distribution by stratified levels of the cumulative dose of neighborhood exposure (Levels 1 to 5) and indicates that approximately 90% of both cases and controls in Level 5 were classified to the same Level 5 of residence-specific exposure. Similarly, in Level 4 of the cumulative dose of residence-specific exposures, over 80% of both cases and controls were classified to the same Level 4 of residence-specific exposure. These findings suggested that just a single residence could contribute to the evaluation of cumulative neighborhood exposure in most subjects (approximately 80–90%). For the relative concentration and duration, there were no substantial differences in distribution between cases and controls in the same exposure levels. However, in relationship to the nearest residence in which a subject lived for at least one year, we did not observe an obvious association with cumulative exposure levels. Moreover, we observed that 26.5% of cases and 22.1% of controls had lived within 500 m of the AC

plant for over a year, and 4.1% of cases and 2.9% of controls had lived more than 2 km from the AC plant for over a year in Level 5, which is supposedly the highest risk group.

Because it is difficult to evaluate various asbestos exposures independently, most studies report risks associated with several combined non-occupational exposures such as neighborhood, domestic, and household. Although few studies of neighborhood exposure have been reported, and there is large heterogeneity among results from those studies, 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 [5]. 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 [15]. Magnani and colleagues conducted a case-control study in Casale, Italy, and showed a significant increased risk of mesothelioma in a population that had only lived in the city, with an OR of 20.6 (95% CI: 6.2–68.6) [16]. 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 [17]. In another 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 [18]. 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) [4]. Classification of non-occupational exposure in existing literature is considerably heterogeneous. For example, different or combined definitions of environmental asbestos exposure have been used in various published studies [19]. However, regardless of the different indicators and the range of categories in those studies, the magnitude of association indicated by OR seems to be fairly consistent with our results.

There were some limitations to our study. First, we observed differences in the types of respondents between cases and controls (Table 1). The highest proportion of respondents among controls was the exposed subject, while the highest proportion of respondents among cases was a spouse or child of the exposed subject. 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 the controls, even though they were spouses and children, were not well informed about details of the indexed 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.

A second limitation was that the consent rate for interviews of the bereaved families of cases seemed to be low (62.1%). However, the psychological effects on bereaved families due to the miserable epidemic of

mesothelioma deaths within a small area in Amagasaki City would also have to be considered. In the municipal administrative reports, there were various reasons for non-consent: 1) unwilling to look back on the past, 2) not well informed about history of the indexed subject, 3) recognized as an industrial compensation, 4) no bereaved families in the city, and 5) other reasons. Although the consent rate was 64.9% among controls when Amagasaki City Government first asked about contact availability, after we sent advance questionnaires to the controls, the consent rate dropped to 39.5%, which is more indicative of a consent rate likely to be observed in a survey of the general population.

Third, 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. Although the mesothelioma diagnosis was not histologically confirmed, the frequency of misclassifications on the cause of mesothelioma deaths qualified by a specialist was thought to be negligible. Fourth, the simulated asbestos concentrations were determined from several assumptions, and the relative numbers ranged from 1 to 10^7 (unit, $1/\text{m}^3$), based on a 10 m x 10 m grid resolution.

The final limitation was that we used cumulative indices of residence-specific exposures to evaluate neighborhood exposure, however, It might be necessary to consider more specific working area of daily living, such as walking to school, gardening, and agricultural working.

A recent world-wide trend assessment for excess risk of mesothelioma deaths using a period analysis from 1996 to 2005 demonstrated a significant increasing rate in Japan of 3.9% annual percent change, with overall quite large disparities between countries [20]. 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 from 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 [14]. 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. 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 of mesothelioma death associated with the 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 during the current study are not openly available due to reasons of sensitivity, because of them including 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, and writing original draft and review & editing. LZ: Data management & analysis, and construction of tables. RL: Data collection and coordination of the interviews. MS: Conceptualization 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. NK: Conceptualization and supervising the study and critical revision of the article. SK: Simulating the relative asbestos concentrations, supervision on 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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Tables

Due to technical limitations, table 1, 2, 3, 4 and 5 is only available as a download in the Supplemental Files section.

Figures

Figure 1

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

- The blue number depicts the simulated relative asbestos concentration [unit: m^{-3}].
- The red letter depicts the straight line distance from the center of premises of the AC plant.

Figure 2

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

Supplementary Files

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