INTRODUCTION

Asbestos is a significant occupational carcinogen and is well established as the only identifiable risk factor for mesothelioma. Several cohort studies have found that the incidence and mortality from mesothelioma were high among asbestos workers employed in mining and asbestos-cement factories, coach and vehicle body builders, shipwrights, and heating and ventilating engineers, among others. However, the magnitude of excess risk due to nonoccupational exposure among the general population in industrial areas is insufficiently estimated. Asbestos is also recognized as a cause of lung cancer. However, because of the prevalence of smoking, the joint relationship between asbestos and smoking on the risk of lung cancer is variable.
According to previous epidemiological studies, the main circumstances for asbestos exposure that have been investigated are as follows: occupational, domestic, and environmental exposure. Occupational exposure occurs among people who are exposed due to work-related activities. Domestic exposure usually occurs among people who live with a person exposed in the workplace, and is thus a result of asbestos fibers brought home by those cohabitants. Another kind of domestic exposure is a result of the use of asbestos material or crushed asbestos material at home. Environmental exposure usually occurs among people who live in the vicinity of a natural source of asbestos or a factory using asbestos. Domestic and environmental exposure could be referred to as nonoccupational exposure in general.\textsuperscript{10,14,15}

In Japan, public awareness of asbestos-related health issues arose in 2005, popularly referred to as the “Kubota Shock”; a report was released that detailed 51 workers who died from asbestos-related diseases during the last 10 years, and 5 residents living near a now-defunct asbestos cement pipe plant of Kubota Kanzaki factory who developed pleural mesothelioma.\textsuperscript{16} The plant was located in Amagasaki City, Hyogo Prefecture, in the southwestern region of Japan (Figure 1), which used a mixture of crocidolite and chrysotile from 1957 to 1975 (referred to hereafter as “the asbestos-use period”).\textsuperscript{17} Moreover, asbestos was also used in relatively smaller quantities at several other factories in the city.\textsuperscript{18} Consequently, residents living in Amagasaki City during the asbestos-use period could be exposed to high levels of asbestos fibers in the air surrounding those factories and thus were particularly considered the subjects in investigating the health effects of asbestos exposure.

To the best of our knowledge, epidemiological studies undertaken to evaluate the risk of asbestos-related diseases in Amagasaki City are few.\textsuperscript{19-23} Considering the typical long latency period of mesothelioma, former estimations need to be updated in order to reflect the latest public health consequences of exposure to asbestos. A population-based cohort study was therefore carried out with the main aim of updating the measure of risk of death from all causes, lung cancer, and mesothelioma associated with exposure to asbestos in Amagasaki City.

\section{Materials and Methods}

\subsection{Long-term residents’ cohort}

The long-term residents’ cohort included 143 929 subjects living in Amagasaki City before 1975 until 2002 aged 40 years or more on January 1, 2002, who were listed on the Basic Resident Registration in Amagasaki City. Subjects were followed up from January 1, 2002, to December 31, 2015, or until the date of death or outmigration, whichever occurred first. The information on date of death or outmigration was obtained from the Basic Resident Registration. Overall, 93 178 subjects were alive at the end of the follow-up period, 38 546 died, and 12 205 migrated.

As the vital status was followed by the Basic Resident Registration at Amagasaki City office, causes of death were ascertained through the Vital Statistics from the National Ministry of Health, Labour and Welfare. Causes of death had been coded according to the International Classification of Diseases, 10th Revision. Lung cancer and mesothelioma deaths were identified using codes C34 and C45, respectively. Because the data were anonymous, the cohort was linked to the Vital Statistics using the following linkage keys: gender, date of birth, and date of death. A total of 20 508 and 18 038 deaths were identified in men and women, respectively: 1953 men and 730 women died from lung cancer and 192 men and 111 women died from mesothelioma during the follow-up period (2002-2015).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Location of Amagasaki City, Japan}
\end{figure}
Person-years, divided into 5-year age groups, were calculated for each individual. Collectively, 66,318 men and 77,611 women in the cohort accumulated 737,079 and 908,814 person-years, respectively, of exposure over the 14 years of follow-up.

2.2 | Short-term residents

The annual population of the whole city was obtained from the official website of Amagasaki City, tabulated by the 5-year age group and gender. Although the data source is not individual, it could be used as the denominator in calculating the death rates of the whole city, after being converted to person-years when multiplied to each annual population by a single calendar year, whereas the numbers of deaths in the whole city from 2002 to 2015 can be obtained from the Vital Statistics, which can be used as numerators in calculating the death rates of the whole city population. We defined short-term residents as subjects living in Amagasaki City who moved into the city after 1975 and attained an age of 40 years or more during follow-up. There were some long-term residents living in Amagasaki City before 1975 until 2002, similar to the subjects in the cohort, but aged less than 40 years on January 1, 2002, and were thus not included in the long-term residents’ cohort. Although these people would reach 40 years or greater during the 14-year follow-up period, they were not included in the short-term residents either, due to their long-term residential history. The number of deaths and person-year counts, within each distinct 5-year age group and sex category, was calculated by subtracting the number of both the long-term residents’ cohort and the relatively younger long-term residents mentioned above from that in the whole city according to each calendar year. A total of 11,020 male and 8,440 female short-term residents died, which accumulated to 854,491 and 871,173 person-years, respectively, during the whole follow-up period.

2.3 | Standardized mortality ratios

The standardized mortality ratio (SMR) was calculated with its 95% confidence interval (CI) for the whole city, and the long-term residents’ cohort compared to the short-term residents according to all-cause deaths, lung cancer, and mesothelioma, by dividing the number of observed deaths by the number of expected deaths that would have occurred. The expected number of deaths was calculated using the Japanese annual sex- and age-specific death rates. These death rates were calculated by dividing the number of deaths by the national population within each 5-year age group and sex category for a calendar year. Both national population and number of deaths were available from the Portal Site of Official Statistics of Japan (e-Stat), also known as a portal site of Japanese Government Statistics. The 95% CIs for SMRs were calculated using the Poisson distribution to determine upper and lower band multipliers applied to the SMR.

In addition, the follow-up was divided into 3 analysis periods: 2002-2006 (5 years), 2007-2011 (5 years), and 2012-2015 (4 years). Stata 14.2/MP (StataCorp, College Station, TX, USA) was used for all statistical analyses, and the level of significance was set at 0.05.

| Age group, years | Whole city | Long-term residents | Short-term residents |
|------------------|------------|---------------------|---------------------|
|                  | No.        | %                   | No.                | %                   |
| Men              |            |                     |                     |                     |
| 40-49            | 26,987     | 23.7                | 9,319              | 14.1                |
| 50-59            | 37,016     | 32.5                | 19,732             | 29.8                |
| 60-69            | 29,671     | 26.0                | 21,285             | 32.1                |
| 70-79            | 15,337     | 13.4                | 11,930             | 18.0                |
| 80-89            | 4,321      | 3.8                 | 3,581              | 5.4                 |
| 90≤              | 732        | 0.6                 | 471                | 0.7                 |
| Total            | 114,064    | 100.0               | 66,318             | 100.0               |
| Women            |            |                     |                     |                     |
| 40-49            | 25,408     | 20.3                | 7,606              | 9.8                 |
| 50-59            | 36,579     | 29.2                | 21,512             | 27.7                |
| 60-69            | 31,439     | 25.1                | 24,094             | 31.0                |
| 70-79            | 20,586     | 16.4                | 15,939             | 20.5                |
| 80-89            | 9,658      | 7.7                 | 7,242              | 9.3                 |
| 90≤              | 1,694      | 1.4                 | 1,218              | 1.6                 |
| Total            | 125,364    | 100.0               | 77,611             | 100.0               |

*Age was calculated at the beginning of 2002.
*Population of short-term residents = population of the whole city – population of long-term residents.

**TABLE 1** Age distribution of all long- and short-term residents of Amagasaki City, Japan, according to gender at the beginning of follow-up
| Age group, years* | Whole city |  |  | Long-term residents |  |  | Short-term residents |  |  |
|------------------|-----------|---|---|---------------------|---|---|---------------------|---|---|
| 2002-2006 (5 years) |  |  |  |  |  |  |  |  |
| 40-49 | 3 152 263 | 371 | 274.3 | 3 156 | 23.3 | 99 | 313.6 | 91 639 | 241 | 263.0 |
| 50-59 | 3 176 382 | 1305 | 739.9 | 82 454 | 46.7 | 591 | 716.8 | 93 928 | 714 | 760.2 |
| 60-69 | 3 151 503 | 2323 | 1 533.3 | 1 02 603 | 67.7 | 1 480 | 1442.5 | 48 900 | 843 | 1723.9 |
| 70-79 | 3 84 745 | 3387 | 3996.7 | 66 337 | 78.3 | 2575 | 3881.7 | 18 408 | 812 | 4411.1 |
| 80-89 | 23 371 | 2372 | 10 149.3 | 19 170 | 82.0 | 1875 | 9781.0 | 4201 | 497 | 11 830.2 |
| 90s | 3712 | 771 | 20 770.5 | 2737 | 73.7 | 614 | 22 434.8 | 975 | 157 | 16 099.5 |
| Total | 5 74 976 | 10 529 | 1 831.2 | 3 048 66 | 53.0 | 7234 | 2372.8 | 2 58 052 | 3264 | 1264.9 |
| 2007-2011 (5 years) |  |  |  |  |  |  |  |  |
| 40-49 | 3 152 094 | 364 | 239.3 | 99 31 | 6.5 | 38 | 382.6 | 1 05 408 | 241 | 228.6 |
| 50-59 | 3 146 647 | 945 | 644.4 | 52 387 | 35.7 | 344 | 656.7 | 94 260 | 601 | 637.6 |
| 60-69 | 3 160 818 | 2413 | 1 500.5 | 90 706 | 56.4 | 1316 | 1450.8 | 70 112 | 1097 | 1564.6 |
| 70-79 | 3 102 916 | 3611 | 3 508.7 | 75 700 | 73.6 | 2498 | 3299.9 | 27 216 | 1113 | 4089.4 |
| 80-89 | 3 277 742 | 3239 | 9882.8 | 25 856 | 78.9 | 2456 | 9498.7 | 6918 | 783 | 11 318.7 |
| 90s | 4039 | 923 | 22 852.2 | 3150 | 78.0 | 731 | 23 205.1 | 889 | 192 | 21 601.3 |
| Total | 5 99 288 | 11 495 | 1 918.1 | 2 577 30 | 43.0 | 7383 | 2864.6 | 3 04 803 | 4027 | 1321.2 |
| 2012-2015 (4 years) |  |  |  |  |  |  |  |  |
| 40-49 | 1 434 754 | 297 | 206.6 | 0 | 0.0 | 0 | NA | 1 03 307 | 218 | 211.0 |
| 50-59 | 1 05 413 | 568 | 538.8 | 24 060 | 22.8 | 165 | 685.8 | 74 465 | 382 | 513.0 |
| 60-69 | 1 28 828 | 1725 | 1339.0 | 57 083 | 44.3 | 798 | 1398.0 | 71 745 | 927 | 1292.1 |
| 70-79 | 96 415 | 3074 | 3188.3 | 63 577 | 65.9 | 1937 | 3046.7 | 32 838 | 1 137 | 3462.5 |
| 80-89 | 35 341 | 3162 | 8947.1 | 26 947 | 76.2 | 2294 | 8512.9 | 8394 | 868 | 10 341.3 |
| 90s | 3703 | 894 | 24 142.6 | 2816 | 76.1 | 697 | 24 749.9 | 887 | 197 | 22 214.1 |
| Total | 5 13 454 | 9720 | 1 893.1 | 1 74 483 | 34.0 | 5891 | 3376.3 | 2 91 636 | 3729 | 1278.6 |
| Total (14 years) |  |  |  |  |  |  |  |  |
| 40-49 | 4 31 111 | 1032 | 239.4 | 41 498 | 9.6 | 137 | 330.1 | 3 00 354 | 700 | 233.1 |
| 50-59 | 4 28 442 | 2818 | 657.7 | 1 58 900 | 37.1 | 1100 | 692.3 | 2 62 653 | 1 697 | 646.1 |
| 60-69 | 4 41 149 | 6461 | 1464.6 | 2 50 391 | 56.8 | 3594 | 1435.4 | 1 90 758 | 2867 | 1503.0 |
| 70-79 | 2 84 076 | 10 072 | 3545.5 | 2 05 613 | 72.4 | 7010 | 3409.3 | 78 463 | 3062 | 3902.5 |
| 80-89 | 91 486 | 8773 | 9589.4 | 71 974 | 78.7 | 6625 | 9204.8 | 19 512 | 2148 | 11 008.4 |
| 90s | 11 454 | 2588 | 22 594.7 | 8703 | 76.0 | 2042 | 23 462.8 | 2751 | 546 | 19 848.4 |
| Total | 16 87 718 | 31 744 | 1 880.9 | 7 37 079 | 43.7 | 20 508 | 2782.3 | 8 54 491 | 11 020 | 1289.7 |

(Continues)
TABLE 2 (Continued)

| Age group, years<sup>a</sup> | Whole city |  | Long-term residents |  | Short-term residents |  |
|-----------------------------|------------|---|---------------------|---|----------------------|---|
|                             | Person-years | No. of deaths | Death rate (per 100 000) | Person-years | %<sup>b</sup> | No. of deaths | Death rate (per 100 000) | Person-years | No. of deaths | Death rate (per 100 000) |
| Women                       |             |               |                        |               |            |              |                        |               |            |                              |
| 2002-2006 (5 years)         |             |               |                        |               |            |              |                        |               |            |                              |
| 40-49                       | 1 27 535    | 160           | 125.5                  | 25 907        | 20.3       | 48           | 185.3                  | 90 756        | 101         | 111.3                              |
| 50-59                       | 1 74 602    | 530           | 303.5                  | 86 113        | 49.3       | 264          | 306.6                  | 88 489        | 266         | 300.6                              |
| 60-69                       | 1 60 002    | 978           | 611.2                  | 1 17 968      | 73.7       | 696          | 590.0                  | 42 034        | 282         | 670.9                              |
| 70-79                       | 1 10 087    | 1980          | 1798.6                 | 86 113        | 78.2       | 1473         | 1710.5                 | 23 974        | 507         | 2 114.8                             |
| 80-89                       | 53 010      | 3006          | 5670.6                 | 40 371        | 76.2       | 2237         | 5541.1                 | 12 639        | 769         | 6084.3                             |
| 90≤                         | 9715        | 1765          | 18 167.8               | 7667          | 78.9       | 1255         | 16 369.0               | 2 048         | 510         | 24 901.8                            |
| Total                       | 6 34 951    | 8419          | 1325.9                 | 3 64 139      | 57.3       | 5973         | 1640.3                 | 2 59 940      | 2435        | 936.8                              |
| 2007-2011 (5 years)         |             |               |                        |               |            |              |                        |               |            |                              |
| 40-49                       | 1 43 929    | 181           | 125.8                  | 8604          | 6.0        | 6            | 69.7                   | 1 01 597      | 135         | 132.9                              |
| 50-59                       | 1 43 498    | 451           | 314.3                  | 47 511        | 33.1       | 149          | 313.6                  | 95 987        | 302         | 314.6                              |
| 60-69                       | 1 69 462    | 987           | 582.4                  | 1 07 386      | 63.4       | 599          | 557.8                  | 62 076        | 388         | 625.0                              |
| 70-79                       | 1 28 547    | 2081          | 1618.9                 | 97 640        | 76.0       | 1488         | 1524.0                 | 30 907        | 593         | 1918.6                             |
| 80-89                       | 64 380      | 3447          | 5354.1                 | 48 399        | 75.2       | 2526         | 5219.2                 | 15 981        | 921         | 5762.9                             |
| 90≤                         | 13 815      | 2511          | 18 175.9               | 10 169        | 73.6       | 1791         | 17 611.7               | 3646         | 720         | 19 749.7                            |
| Total                       | 6 63 631    | 9658          | 1455.3                 | 3 19 708      | 48.2       | 6559         | 2051.6                 | 3 10 195      | 3059        | 986.2                              |
| 2012-2015 (4 years)         |             |               |                        |               |            |              |                        |               |            |                              |
| 40-49                       | 1 36 800    | 139           | 101.6                  | 0            | 0.0        | 0            | NA                     | 99 057        | 89          | 89.8                               |
| 50-59                       | 1 03 242    | 247           | 239.2                  | 20 424        | 19.8       | 68           | 332.9                  | 76 358        | 172         | 225.3                              |
| 60-69                       | 1 36 009    | 777           | 571.3                  | 65 114        | 47.9       | 366          | 562.1                  | 70 895        | 411         | 579.7                              |
| 70-79                       | 1 16 481    | 1658          | 1423.4                 | 82 702        | 71.0       | 1100         | 1330.1                 | 33 779        | 558         | 1651.9                             |
| 80-89                       | 62 981      | 3201          | 5082.5                 | 46 173        | 73.3       | 2251         | 4875.2                 | 16 808        | 950         | 5 652.0                             |
| 90≤                         | 14 695      | 2487          | 16 924.1               | 10 553        | 71.8       | 1721         | 16 307.5               | 4142         | 766         | 18 495.4                            |
| Total                       | 5 70 208    | 8509          | 1492.3                 | 2 24 967      | 39.5       | 5506         | 2447.5                 | 3 01 038      | 2946        | 978.6                              |
| Total (14 years)            |             |               |                        |               |            |              |                        |               |            |                              |
| 40-49                       | 4 08 264    | 480           | 117.6                  | 34 511        | 8.5        | 54           | 156.5                  | 2 91 411      | 325         | 111.5                              |
| 50-59                       | 4 21 342    | 1 228         | 291.4                  | 1 54 047      | 36.6       | 481          | 312.2                  | 2 60 834      | 740         | 283.7                              |
| 60-69                       | 4 65 473    | 2 742         | 589.1                  | 2 90 468      | 62.4       | 1 661        | 571.8                  | 1 75 005      | 1081        | 617.7                              |
| 70-79                       | 3 55 115    | 5 719         | 1610.5                 | 2 66 456      | 75.0       | 4061         | 1524.1                 | 88 659        | 1658        | 1870.1                             |
| 80-89                       | 1 80 371    | 9 654         | 5352.3                 | 1 34 942      | 74.8       | 7014         | 5197.8                 | 45 429        | 2640        | 5811.3                             |
| 90≤                         | 38 225      | 6 763         | 17 692.6               | 28 390        | 74.3       | 4767         | 16 791.3               | 9835          | 1996        | 20 294.4                            |
| Total                       | 18 68 790   | 26 586        | 1422.6                 | 9 08 814      | 48.6       | 18 038       | 1 984.8                 | 8 71 173      | 8440        | 968.8                              |

<sup>a</sup>Age group was categorized by the attained age.

<sup>b</sup>% = person-years of cohort/person-years of the whole city × 100.

NA, not available.
P-value of <.05. Informed consent was waived because official data were used. The study protocol was approved by the Institutional Review Board of Osaka University (Suita, Japan).

3 | RESULTS

Age distribution of the whole city, long-, and short-term residents according to gender at the beginning of the follow-up period is shown in Table 1. A total of 66 318 men and 77 611 women aged 40 years or more were included in the long-term residents’ cohort, whereas 47 746 men and 47 753 women were included in the short-term residents. In the long-term residents’ cohort, the subjects were mainly distributed in the 50- to 79-year age group. In contrast, the majority of short-term residents were aged 40-59 years. No significant gender differences in age distribution could be observed in the long- or short-term residents.

Table 2 presents the person-years, number of deaths, and death rate (per 100 000) of all-cause death by 10-year age groups and gender among the whole city and long- and short-term residents. The total person-years decreased in the long-term residents’ cohort, but increased in the short-term residents over 3 analysis periods. The decreasing trend in the long-term residents’ cohort could be explained by death or outmigration. Furthermore, as people younger than 40 years were excluded in the cohort, there was no younger generation under 40 years of age that could move to the older age group over the follow-up period. By contrast, the increasing trend in the short-term residents was observed due to the presence of both immigration and outmigration. As a result, the age distribution was different between the long- and short-term residents. In total, the proportions of long-term residents’ cohort to the whole city, in person-years, decreased from 53.0% to 34.0% in men and 57.3% to 39.5% in women over 3 analysis periods. When we focused on those proportions by age group within each analysis period, the age group with a high proportion of long-term residents was found to be elderly people, particular those aged over 70 years. With regard to the total death rate over 3 analysis periods, the death rate of long-term residents increased from 2372.8 to 3376.3 in men, and from 1640.3 to 2447.5 in women, whereas no significant changes were observed among short-term residents.

The SMRs are shown in Table 3, according to causes of death among the whole city and long- and short-term residents by period and gender. The overall SMRs of mesothelioma in the long-term residents’ cohort were 6.75 in men and 14.99 in women, which was markedly increased compared to the short-term residents. The SMRs of mesothelioma in short-term residents were also higher than that of the national level, namely 3.45 in men and 5.40 in women. Furthermore, women presented a notably higher SMR for mesothelioma than men, observed in both the long- and short-term residents. In addition, the SMR of mesothelioma in the long-term residents’ cohort had an increasing trend in women across the subperiod of follow-up. Moreover, the results for mesothelioma, lung cancer, and all-cause deaths showed a small but significant extent of excess mortality, representing the SMRs of 1.28 in men and 1.23 in women for lung cancer, and 1.12 in men and 1.07 in women for all-cause deaths in the cohort. Furthermore, these 2 causes of death showed a relatively lower SMR in the long-term residents’ cohort than in the short-term residents. However, no gender differences were noted in lung cancer or all-cause deaths.

4 | DISCUSSION

4.1 | Mesothelioma

We observed that in the long-term residents’ cohort 6.75 times more men and 14.99 times more women, compared to their age-mates in the national general population, died of mesothelioma, which is consistent with the findings of other earlier studies in Amagasaki City.19,21,23 A large amount of asbestos was processed in the manufacturing plants in Amagasaki City from 1957 to 1975.18 Thus, more residents in Amagasaki City were employed in those asbestos-related factories, which predominantly consisted of male workers who were occupationally exposed to asbestos. As a consequence, the frequency of subjects who had an experience of occupational exposure to asbestos was higher in the long-term residents’ cohort, compared to the national general population. This is the reason why SMRs increased in the long-term residents’ cohort, in particular for men who were more likely to have experienced occupational exposure.

The present study showed a higher excess of mesothelioma among women than men in the long-term residents’ cohort. This can be partly explained due to the difference in national rates between men and women. The national rates in men are higher than those in women due to the predominant frequent occupational exposure to asbestos among men compared to women. However, due to the concentration of asbestos-related factories in Amagasaki City, asbestos fibers suspended in the air could be inhaled by people living in the neighborhood of those factories.1,19 Therefore, the risk of mesothelioma could arise from environmental exposure to asbestos. In addition, because of the high frequency of asbestos-related workers in the city, more people who were living with those workers might be exposed to asbestos fibers brought home by them. As a result, the risk of mesothelioma could arise from domestic exposure to asbestos as well. Hence, the notably higher SMRs shown in women, the vast majority of whom were less likely to be occupationally exposed, suggested that a substantial proportion of mesothelioma cases were attributable to non-occupational asbestos exposure among women in Amagasaki City, which is much higher than the national level. There remains the possibility that the increased SMRs could be affected by the occupational exposure to asbestos among women as well, although the impact would be limited compared to that among men.

When the cohort was separately analyzed for each period, SMRs of mesothelioma were found to be almost unchanged in men (from 6.26 to 6.96), but were increased in women (from 11.77 to 18.03). The difference in trend between men and women could be
TABLE 3  Standardized mortality ratios according to causes of death by period and gender among all long- and short-term residents in Amagasaki City, Japan

| Cause of death | Period       | Whole city | Long-term residents | Short-term residents |
|----------------|--------------|------------|---------------------|----------------------|
|                |              | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          |
|                |              | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          |
|                |              | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          |
|                |              | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          |
|                |              | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          | Observed deaths | Expected deaths | SMR 95% CI          |

**Men**

All causes
- 2002-2006: 10 529 / 8 902.49 = 1.18 (1.16-1.21)
- 2007-2011: 11 495 / 9 715.26 = 1.18 (1.16-1.21)
- 2012-2015: 9720 / 8 505.92 = 1.14 (1.12-1.17)
- Total: 31 744 / 27 123.67 = 1.17 (1.16-1.18)

Lung cancer
- 2002-2006: 947 / 722.11 = 1.31 (1.23-1.40)
- 2007-2011: 1089 / 816.60 = 1.33 (1.26-1.42)
- 2012-2015: 864 / 710.16 = 1.22 (1.14-1.30)
- Total: 2900 / 2 248.87 = 1.29 (1.24-1.34)

Mesothelioma
- 2002-2006: 61 / 12.09 = 5.05 (3.86-6.48)
- 2007-2011: 97 / 16.35 = 5.93 (4.81-7.24)
- 2012-2015: 90 / 16.12 = 5.58 (4.49-6.86)
- Total: 248 / 44.56 = 5.57 (4.89-6.30)

**Women**

All causes
- 2002-2006: 8419 / 7 485.23 = 1.12 (1.10-1.15)
- 2007-2011: 9658 / 8 502.00 = 1.14 (1.11-1.16)
- 2012-2015: 8509 / 7 967.62 = 1.07 (1.05-1.09)
- Total: 26 586 / 23 954.84 = 1.11 (1.10-1.12)

Lung cancer
- 2002-2006: 329 / 266.85 = 1.23 (1.10-1.15)
- 2007-2011: 399 / 308.90 = 1.29 (1.17-1.42)
- 2012-2015: 390 / 288.40 = 1.35 (1.22-1.49)
- Total: 1118 / 864.15 = 1.29 (1.22-1.37)

Mesothelioma
- 2002-2006: 33 / 3.63 = 9.10 (6.26-12.77)
- 2007-2011: 49 / 3.68 = 13.32 (9.85-17.60)
- 2012-2015: 47 / 3.51 = 13.40 (9.84-17.81)
- Total: 129 / 10.81 = 11.93 (9.96-14.18)

CI, confidence interval; SMR, standardized mortality ratio.
explained by the changes in the national rate. The asbestos-use period in Amagasaki City was supposed to be almost the same as that in the nationwide. Moreover, the death rate for men in the cohort increased throughout the follow-up, which was in accordance with the nationwide data. Thus, the SMR in men could remain constant. In contrast, the national rate for women was maintained at a low level because the nonoccupational exposure to asbestos is seldom assessed all over the country. However, the death rate for women was increasing in the cohort throughout the follow-up period. As a result, the increasing trend of SMR occurred among women in the long-term residents’ cohort.

When we compared the SMRs between the long- and the short-term residents, the SMRs for mesothelioma were remarkably higher among the long-term residents. This suggested that long-term residents who lived in Amagasaki City during the exposure period suffered from mesothelioma. Moreover, a significant excess in mesothelioma mortality was also found among the short-term residents’ population. Nine out of 11 persons who died of mesothelioma were short-term residents during 2002-2006, and were found to have had a history of residence in Amagasaki City before the end of 1975. Therefore, the short-term residents were actually a mixed group, including re-migrants with high exposure to asbestos in the past and new migrants with average exposure at the national level.

4.2 | Lung cancer

A significantly increased risk of death from lung cancer was also observed in the long-term residents’ cohort compared to the national general population. Furthermore, the risk in the long-term residents’ cohort was found to be lower than that in short-term residents, which is different from the result in mesothelioma. If the excess mortality for lung cancer in the long-term residents’ cohort was affected by exposure to asbestos, their SMRs should be higher than among the short-term residents. Thus, the higher SMR in short-term residents implied that the excesses in lung cancer attributed to other risk factors rather than exposure to asbestos in the present study. The relationship between asbestos exposure and lung cancer risk has long been studied and is complicated, mainly because both smoking and asbestos exposure are important risk factors for lung cancer and even have a multiplicative effect when combined. In addition, Amagasaki City was an air pollution designated area, which is another risk factor of lung cancer. Thus, information on smoking status and air pollution is required to explain the lung cancer excess mortality.

4.3 | All causes

Similar to the results in lung cancer, although the SMRs from all causes were higher both in the long- and short-term residents than those at the national level, people in the long-term residents’ cohort had a relatively lower mortality compared to the short-term residents. Therefore, excesses in all-cause mortality could be attributed to other risk factors rather than exposure to asbestos alone. The risk factors that can be considered include not only lifestyle habits in general, such as smoking, alcohol consumption, or obesity, but also the social capital of the local community.

The main strength of this study is the long duration measured as the length of time from onset of exposure to the occurrence of mesothelioma. The latency of mesothelioma between initial time of exposure to asbestos and the onset of disease is typically longer than 30 years. In the present study, the length of this duration was up to a maximum of 59 years, so that more cases of mesothelioma could be detected. Another advantage of our study is that mortality in the long-term residents’ cohort was investigated using the official data at an individual level, which has not been executed so far. Moreover, the long- and short-term residents were also compared, which helps in understanding the contribution of exposure to asbestos in different causes of death.

Nevertheless, the study design has some limitations. First, non-occupational asbestos exposure alone was not separated from occupational exposure. Because information on occupational history cannot be obtained in the official data, the subjects who might be exposed to occupational asbestos were included in the long-term residents’ cohort. Moreover, deaths due to occupational asbestos exposure cannot be excluded with the use of the national mortality rates. Thus, a case-control study nested within the long-term residents’ cohort is ongoing. Another limitation was that some unmeasured confounders, such as smoking habits and air pollution, could exist. Thus, exposure to asbestos might not be the only risk factor to explain the differences in SMR between long- and short-term residents or between Amagasaki City and nationwide.

In conclusion, the present study provides updated quantitative information on the risk of mesothelioma and lung cancer in a unique urban area where the asbestos-related factories were concentrated in Japan. The increased SMR of mesothelioma suggests the impact of occupational asbestos exposure among men and nonoccupational asbestos exposure among women in the long-term residents’ cohort. In addition, a high level of excess mortality from mesothelioma persists, despite the mixture of crocidolite and chrysotile not being used for three or four decades. Further studies are needed to refine our understanding in the future.

ACKNOWLEDGMENTS

This study was supported by the Japan Society for the Promotion of Science KAKENHI Grant Number 15H04774. The authors would like to thank all the staff at Amagasaki City Public Health Center for their much-appreciated help in preparing the data and to Ms. Kazumi Inamura, Mayor of Amagasaki City, the staff at Amagasaki City Environmental Protection Section, Mr. Goro Asano, and Mr. Hiroshi Iida for their support and invaluable comments and suggestions.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.
REFERENCES

1. World Health Organization. Elimination of asbestos-related diseases 2006. http://apps.who.intiris/bitstream/handle/10665/69479/?sequence=1. Accessed September 13, 2018.

2. Piolatto G, Negri E, La Vecchia C, Pira E, Decarli A, Petro J. An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. Occup Environ Med. 1990;47:810-814.

3. McDonald J, Liddell F, Dufresne A, McDonald A. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. Occup Environ Med. 1993;50:1073-1081.

4. Tulpinsky TH, Ginsberg GM, Iscovich J, Shihab S, Fischbein A, Richter ED. Cancer in ex-asbestos cement workers in Israel, 1953–1992. Am J Ind Med. 1999;35:1-8.

5. Ulvestad B, Kjarheim K, Martinsen JI, et al. Cancer incidence among workers in the asbestos-cement producing industry in Norway. Scand J Work Environ Health. 2002;28(6):411-417.

6. Coggon D, Harris EC, Brown T, Rice S, Palmer KT. Occupational Mortality in England and WALES, 1991-2000. London: Office of Public Sector Information; 2009.

7. Petro J, Rake C, Gilham C, Hatch J. Occupational, domestic and environmental mesothelioma risks in Britain. A case–control study. RR696 research report. Norwich: HSE Books; 2009. http://www.hse.gov.uk/research/rrpdf/rr696.pdf. Accessed September 13, 2018.

8. Andersen AB. Worker Safety in the Ship-Breaking Industries. Geneva: International Labour Office; 2001.

9. Henderson DW, Rödelperger K, Woitowitz HJ, Leigh J. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997-2004. Pathology. 2004;36:517-550.

10. Bourdès V, Boffetta P, Pisani P. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. Eur J Epidemiol. 2000;16:411-417.

11. Saracci R. Asbestos and lung cancer: an analysis of the epidemiological evidence on the asbestos—smoking interaction. Int J Cancer. 1977;20:323-331.

12. Vainio H, Boffetta P. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Scand J Work Environ Health. 1994;20:235-242.

13. Goodman M, Morgan RW, Ray R, Malloy CD, Zhao K. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. Cancer Causes Control. 1999;10:453-465.

14. Mirabelli D, Cavone D, Merler E, et al. Non-occupational exposure to asbestos and malignant mesothelioma in the Italian National Registry of Mesotheliomas. Occup Environ Med. 2010;67:792-794.

15. Magnani C, Agudo A, Gonzalez C, et al. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. Br J Cancer. 2000;83:104.

16. Ohshima H. Five cases with mesothelioma living near a now-defunct asbestos cement plant in Amagasaki city, [in Japanese]. Mainichi Newspaper. 2005 June 29: 1.

17. Corporation K. Corporate Data of Employees with Asbestos-Related Diseases in Kanzi Plant, A Now-Defunct Asbestos Cement Plant in Amagasaki City, Hyogo, JP: Kubota Corporation; 2005.

18. Amagasaki City. A Report on the Amount of Asbestos Used in the Past by 136 Companies in Amagasaki City, Amagasaki, Hyogo Prefecture. Amagasaki, Japan: City Printing Office; 2006.

19. Kurumatan N, Kamagai S. Mapping the risk of mesothelioma due to neighborhood asbestos exposure. Am J Respir Crit Care Med. 2008;178:624-629.

20. Ministry of the Environment. Report of the survey on health impact of exposure to asbestos in Hyogo Prefecture [Government Publication], [in Japanese], Tokyo, JP: Ministry of the Environment; 2006. http://www.env.go.jp/press/files/jp/8031.pdf. Accessed September 21, 2018.

21. Ministry of the Environment. Report of the epidemiological study on exposure to asbestos in Amagasaki City [Government Publication], [in Japanese], Tokyo, JP: Ministry of the Environment; 2007. http://www.env.go.jp/air/asbestos/commi_hefc/rep_h18/01.pdf. Accessed September 21, 2018.

22. Kamagai 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;52:790-798.

23. Nakaya T. Uncovering geographic concentrations of elevated mesothelioma risks across Japan: spatial epidemiological mapping of the asbestos-related disease. Geographical Reports of Tokyo Metropolitan University, 2015; 50: 45-53.

24. Amagasaki City. The population of Amagasaki City [in Japanese]. 2002-2015. http://www.city.amagasaki.hyogo.jp/shisei/sogo_annai/toukei/012ama_jinko_0/index.html. Accessed July 22, 2018.

25. Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer new findings from the North American insulator cohort. Am J Respir Crit Care Med. 2013;188:90-96.

26. Gustavsson P, Nyberg F, Pershagen G, Schéle P, Jakobsson R, Plato N. Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. Am J Epidemiol. 2002;155:1016-1022.

27. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. Lancet. 2005;366:397-408.

How to cite this article: Zha L, Kitamura Y, Kitamura T, et al. Population-based cohort study on health effects of asbestos exposure in Japan. Cancer Sci. 2019;110:1076-1084. https://doi.org/10.1111/cas.13930