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Population-based cohort study on health effects of asbestos exposure in Japan

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Occupational asbestos exposure occurs in many workplaces and is a well-known cause of mesothelioma and lung cancer. However, the association between nonoccupational asbestos exposure and those diseases is not clearly described. The aim of this study was to investigate cause-specific mortality among the residents of Amagasaki, a city in Japan with many asbestos factories, and evaluate the potential excess mortality due to established and suspected asbestos-related diseases. The study population consisted of 143 929 residents in Amagasaki City before 1975 until 2002, aged 40 years or older on January 1, 2002. Follow-up was carried out from 2002 to 2015. Standardized mortality ratio (SMR) with its 95% confidence interval (CI) was calculated by sex, using the mortality rate of the Japanese population as reference. A total of 38 546 deaths (including 303 from mesothelioma and 2683 from lung cancer) were observed. The SMRs in the long-term residents' cohort were as follows: death due to all causes, 1.12 (95% CI, 1.10-1.13) in men and 1.07 (95% CI, 1.06-1.09) in women; lung cancer, 1.28 (95% CI, 1.23-1.34) in men and 1.23 (95% CI, 1.14-1.32) in women; and mesothelioma, 6.75 (95% CI, 5.83-7.78) in men and 14.99 (95% CI, 12.34-18.06) in women. These SMRs were significantly higher than expected. 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, the high level of excess mortality from mesothelioma has persisted, despite the mixture of crocidolite and chrysotile no longer being used for three or four decades.

KEYWORDS
asbestos, cohort study, lung cancer, mesothelioma, standardized mortality ratio

1 | INTRODUCTION

Asbestos is a significant occupational carcinogen and is well established as the only identifiable risk factor for mesothelioma.[1] 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.[2-9] However, the magnitude of excess risk due to nonoccupational exposure among the general population in industrial areas is insufficiently estimated.[10] 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.[11-13]

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.[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.[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").[17] Moreover, asbestos was also used in relatively smaller quantities at several other factories in the city.[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.[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.

2 | MATERIALS AND METHODS

2.1 | 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).

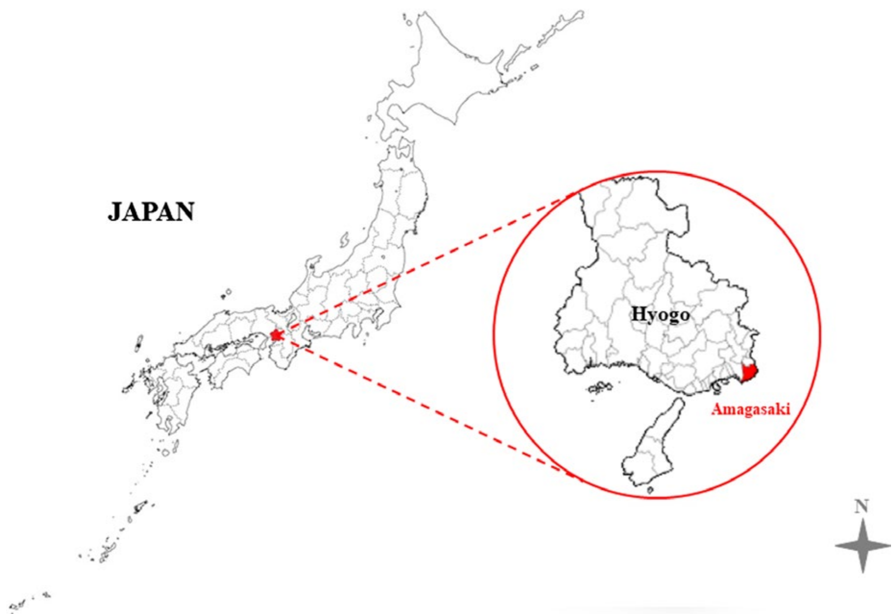

FIGURE 1 Location of Amagasaki City, Japan

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.[24] 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 8440 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

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[a]	Whole city		Long-term residents		Short-term residents	
	No.	%	No.	%	No.[b]	%
Men						
40-49	26 987	23.7	9319	14.1	17 668	37.0
50-59	37 016	32.5	19 732	29.8	17 284	36.2
60-69	29 671	26.0	21 285	32.1	8386	17.6
70-79	15 337	13.4	11 930	18.0	3407	7.1
80-89	4321	3.8	3581	5.4	740	1.5
90≤	732	0.6	471	0.7	261	0.5
Total	114 064	100.0	66 318	100.0	47 746	100.0
Women						
40-49	25 408	20.3	7606	9.8	17 802	37.3
50-59	36 579	29.2	21 512	27.7	15 067	31.6
60-69	31 439	25.1	24 094	31.0	7345	15.4
70-79	20 586	16.4	15 939	20.5	4647	9.7
80-89	9658	7.7	7242	9.3	2416	5.1
90≤	1694	1.4	1218	1.6	476	1.0
Total	125 364	100.0	77 611	100.0	47 753	100.0

[a]Age was calculated at the beginning of 2002.

[b]Population of short-term residents = population of the whole city − population of long-term residents.

TABLE 2 Person-years, number of all-cause deaths, and death rate according to age group and gender among all long- and short-term residents in Amagasaki City, Japan

	Whole city			Long-term residents				Short-term residents		
Age group, years[a]	Person-years	No. of deaths	Death rate (per 100 000)	Person-years	%[b]	No. of deaths	Death rate (per 100 000)	Person-years	No. of deaths	Death rate (per 100 000)
Men										
2002-2006 (5 years)										
40-49	1 35 263	371	274.3	31 566	23.3	99	313.6	91 639	241	263.0
50-59	1 76 382	1305	739.9	82 454	46.7	591	716.8	93 928	714	760.2
60-69	1 51 503	2323	1533.3	1 02 603	67.7	1480	1442.5	48 900	843	1723.9
70-79	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
90≤	3712	771	20 770.5	2737	73.7	614	22 434.8	975	157	16 099.5
Total	5 74 976	10 529	1831.2	3 04 866	53.0	7234	2372.8	2 58 052	3264	1264.9
2007-2011 (5 years)										
40-49	1 52 094	364	239.3	9931	6.5	38	382.6	1 05 408	241	228.6
50-59	1 46 647	945	644.4	52 387	35.7	344	656.7	94 260	601	637.6
60-69	1 60 818	2413	1500.5	90 706	56.4	1316	1450.8	70 112	1097	1564.6
70-79	1 02 916	3611	3508.7	75 700	73.6	2498	3299.9	27 216	1113	4089.4
80-89	32 774	3239	9882.8	25 856	78.9	2456	9498.7	6918	783	11 318.7
90≤	4039	923	22 852.2	3150	78.0	731	23 205.1	889	192	21 601.3
Total	5 99 288	11 495	1918.1	2 57 730	43.0	7383	2864.6	3 04 803	4027	1321.2
2012-2015 (4 years)										
40-49	1 43 754	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
90≤	3703	894	24 142.6	2816	76.1	697	24 749.9	887	197	22 214.1
Total	5 13 454	9720	1893.1	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
90≤	11 454	2588	22 594.7	8703	76.0	2042	23 462.8	2751	546	19 848.4
Total	16 87 718	31 744	1880.9	7 37 079	43.7	20 508	2782.3	8 54 491	11 020	1289.7

(Continues)

TABLE 2 (Continued)

Age group, years[a]	Whole city			Long-term residents				Short-term residents		
	Person-years	No. of deaths	Death rate (per 100 000)	Person-years	%[b]	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

[a]Age group was categorized by the attained age.
[b]% = 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 inmigration 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

		Whole city				Long-term residents				Short-term residents			
Cause of death	Period	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	7234	6 402.95	1.13	1.10-1.16	3264	2 479.01	1.32	1.27-1.36
	2007-2011	11 495	9 715.26	1.18	1.16-1.21	7383	6 572.50	1.12	1.10-1.15	4027	3 075.76	1.31	1.27-1.35
	2012-2015	9720	8 505.92	1.14	1.12-1.17	5891	5 378.13	1.10	1.07-1.12	3729	3 036.84	1.23	1.19-1.27
	Total	31 744	27 123.67	1.17	1.16-1.18	20 508	18 354	1.12	1.10-1.13	11 020	8591.61	1.28	1.26-1.31
Lung cancer	2002-2006	947	722.11	1.31	1.23-1.40	680	525.62	1.29	1.20-1.39	265	195.81	1.35	1.20-1.53
	2007-2011	1089	816.60	1.33	1.26-1.42	736	555.31	1.33	1.23-1.42	348	258.89	1.34	1.21-1.49
	2012-2015	864	710.16	1.22	1.14-1.30	537	442.16	1.21	1.12-1.32	320	263.95	1.21	1.08-1.35
	Total	2900	2 248.87	1.29	1.24-1.34	1953	1 523.09	1.28	1.23-1.34	933	718.65	1.30	1.22-1.38
Mesothelioma	2002-2006	61	12.09	5.05	3.86-6.48	52	8.31	6.26	4.77-8.21	9	3.77	2.39	1.09-4.53
	2007-2011	97	16.35	5.93	4.81-7.24	73	10.51	6.95	5.52-8.74	24	5.78	4.15	2.66-6.18
	2012-2015	90	16.12	5.58	4.49-6.86	67	9.62	6.96	5.48-8.85	22	6.39	3.44	2.16-5.21
	Total	248	44.56	5.57	4.89-6.30	192	28.44	6.75	5.83-7.78	55	15.94	3.45	2.60-4.49
Women													
All causes	2002-2006	8419	7 485.23	1.12	1.10-1.15	5973	5 513.07	1.08	1.06-1.11	2435	1 962.83	1.24	1.19-1.29
	2007-2011	9658	8 502.00	1.14	1.11-1.16	6559	6038.99	1.09	1.06-1.11	3059	2429.99	1.26	1.21-1.30
	2012-2015	8509	7 967.62	1.07	1.05-1.09	5506	5 274.89	1.04	1.02-1.07	2946	2 645.38	1.11	1.07-1.15
	Total	26 586	23 954.84	1.11	1.10-1.12	18 038	16 827	1.07	1.06-1.09	8440	7038.20	1.20	1.17-1.23
Lung cancer	2002-2006	329	266.85	1.23	1.10-1.37	237	195.39	1.21	1.07-1.38	92	71.18	1.29	1.04-1.59
	2007-2011	399	308.90	1.29	1.17-1.42	255	215.35	1.18	1.05-1.34	143	92.53	1.55	1.30-1.82
	2012-2015	390	288.40	1.35	1.22-1.49	238	183.27	1.30	1.14-1.47	150	103.49	1.45	1.23-1.70
	Total	1118	864.15	1.29	1.22-1.37	730	594.01	1.23	1.14-1.32	385	267.20	1.44	1.30-1.59
Mesothelioma	2002-2006	33	3.63	9.10	6.26-12.77	31	2.63	11.77	8.28-16.74	2	0.99	2.03	0.24-7.30
	2007-2011	49	3.68	13.32	9.85-17.60	39	2.50	15.63	11.42-21.39	10	1.17	8.58	4.10-15.72
	2012-2015	47	3.51	13.40	9.84-17.81	41	2.27	18.03	13.27-24.48	6	1.18	5.07	1.87-11.07
	Total	129	10.81	11.93	9.96-14.18	111	7.40	14.99	12.34-18.06	18	3.34	5.40	3.19-8.52

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.[25,26] 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.[27] 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, nonoccupational 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.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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