whether a caregiver feels burdened in a particular situation depends on their ability to cope with stressful situations.[11,12]

With respect to the ability to cope with stress, Antonovsky proposed sense of coherence (SOC) as an important factor for health enhancement based on the results of research in highly motivated and healthy middle-aged and older people under stressful conditions.[13] According to Antonovsky's conceptualization, SOC has three components: comprehensibility, manageability and meaningfulness. Comprehensibility refers to people's ability to realize that their situation is understandable and/or predictable. Manageability refers to people's perception of their ability to cope with a difficult situation. Lastly, meaningfulness is the ability to find meaning in everyday events and/or in problems confronted.

Recently, it has been reported that the relationship between strong SOC and better health exists in various countries and ethnic/cultural groups.[14–16] Among caregivers for terminally ill cancer patients, but not for dementia patients, a strong SOC has been shown to mediate the effects of caregiving stressors, appraisals of caregiving confidence, and subjective caregiving burden on caregivers' depressive distress.[17] It is believed that those with a strong SOC are better able to cope with difficult situations as caregivers, which can have a positive impact on dementia patients.[18–20]

Hospital-based studies may provide a biased representation of caregiver's burden. Because extreme BPSD will motivate caregivers to take their charge to a hospital, the caretaker who visits the hospital would likely feel a greater burden and weakened self-esteem. Therefore, we aimed to explore in this epidemiological study whether a significant relationship exists between caregiver burden and SOC.

METHODS

Participants and procedures

We randomly selected 1000 community residents aged 65 years old and older who lived in Omuta City, Japan, from a nationwide dementia prevalence study. Participants were admitted to the survey between January 2012 and November 2012. Among the 1000 residents selected, 511 elderly participated. And of these 511 participants, 274 who participated in the study with a family member or caregiver were subjected to an investigation. A total of 229 subjects and their family members/caregivers who did not have missing data values were included in the statistical analyses. The procedure for enrolment of the participants is shown in Figure 1. Caregivers for subjects with mild cognitive impairment and dementia ($n = 78$) were included in the statistical analysis to assess the relationship between burden and SOC.

Participants were sent a study invitation that instructed them to visit a municipal facility to participate in the study and undergo neurocognitive and medical examinations. In cases where the examinee could not visit a study site, a physician and a healthcare professional visited the residence and conducted the interview. Interviews and neurocognitive testing were performed by well-trained clinical psychologists, social welfare counsellors, or nurses. A neurologist or psychiatrist then performed a physical examination and were responsible for diagnosing dementia. When it was difficult to reach a diagnosis, several doctors diagnosed the subjects using magnetic resonance imaging.

In order to assess cognitive function, we used the Japanese version of the Mini-Mental State

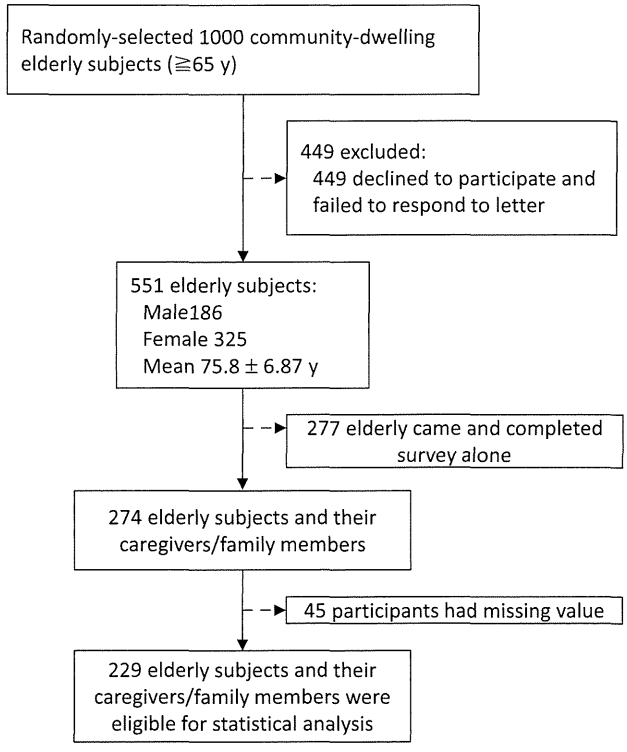

Figure 1 Enrolment of participants. y, years.

Examination (MMSE) and the logical memory scale (I) of the Wechsler Memory Scale-Revised.[21–24] Among cases in which dementia was suspected based on the results of these two neuropsychological tests, the Geriatric Depression Scale was used to assess depression in the elderly,[25] and the Psychogeriatric Assessment Scale was used to assess cognitive impairment due to depression or stroke.[26] In cases where a more in-depth examination was necessary, cerebral magnetic resonance imaging was performed to determine the type of dementia.

Caregivers and family members who attended with the study participants were assessed using the Zarit Caregiver Burden Interview (ZBI),[27–29] the 13-item SOC scale,[30] and the Clinical Dementia Rating (CDR),[31] which is a standardized clinical dementia staging instrument. This study was approved by the Human Ethics Review Committee of Kumamoto University (Number 491) (Kumamoto, Japan). All participants and caregivers provided written informed consent before participating in this study.

Measurements

The MMSE is a one of the most frequently used assessment methods for the estimation of cognitive function, and it has been shown to have adequate reliability and validity.[22] The Japanese version of the MMSE, which has a maximum score of 30 points, consists of 10 cognitive function domains. A higher score on the MMSE reflects better cognitive function.

The CDR is a widely used observational method for the assessment of dementia severity. The CDR consists of six domains for cognitive and functional performance in relation to dementia; global severity scoring is classified as non-dementia (CDR 0), mild cognitive impairment or questionable dementia (CDR 0.5), mild dementia (CDR 1), moderate dementia (CDR 2), and severe dementia (CDR 3).

Caregiver burden was assessed using the short, eight-item Japanese version of the ZBI developed by Arai *et al*.[27] The eight items were assessed on a 5-point Likert scale, ranging from 0 (never) to 4 (nearly always). The total score for this scale ranged from 0 to 32 points, with higher scores indicating increased caregiver burden. The validity and reliability of this test have been well established in previous studies.[28,29]

The ability to cope with stress was evaluated using the 13-item SOC scale. For each of the 13 questions, a family member or caregiver was asked to provide an answer on a 7-point scale with two anchoring phrases, 'very often' (1) and 'very seldom or never' (7). The total SOC score ranged from 13 to 91, with a higher score reflecting a stronger SOC. The 13-item version of the SOC scale has been shown to have adequate reliability and validity.[30,32]

Statistical analyses

Pearson's correlation and multiple linear regression were used for data analysis. We applied the stepwise procedure to identify related variables for inclusion in regression models ($P < 0.05$). All statistical analyses were performed using SPSS Statistics 20.0.0.1 statistical software (IBM Corporation, Armonk, NY, USA). A two-tailed *P*-value of less than 0.05 was considered significant.

RESULTS

The characteristics of participants and information regarding dementia are summarized in Table 1. The mean age of the 229 impaired elderly subjects was 74.0 ± 7.0 years, and 94 of the participants were men (41.0%). Of the 229 subjects, 53 (23.1%) were diagnosed with mild cognitive impairment, 16 (7.0%) with Alzheimer's disease, 4 (1.7%) with vascular dementia, 2 (0.9%) with dementia with Lewy bodies, 1 (0.4%) with Parkinson's disease with dementia, and 1 (0.4%) with frontotemporal dementia. The rate of CDR equal to or greater than 0.5 in the sample was 34.1%; the CDR informant was typically the subject's spouse (65.9%).

Table 2 shows Pearson's correlation coefficients for relationships between background information, cognitive function, stress-coping ability, and caregiver burden among the 78 caregivers and/or family members. The ZBI score was significantly associated with the SOC score ($r = -0.38$, $P < 0.001$). Multiple linear regression analysis revealed that the SOC score ($\beta = -0.42$, $P < 0.001$) and MMSE score ($\beta = -0.28$, $P = 0.009$) were significantly associated with the ZBI score ($F_{(2, 76)} = 10.51$, $P < 0.001$) (Table 3).

To more closely examine the association between stress coping ability and caregiver burden, we performed multiple linear regression analysis with the SOC score as the dependent variable and with sex, age, years of education, MMSE score, and ZBI score as independent variables (stepwise method). As shown in Table 4, decreased personal strain in the ZBI was significantly associated with a high SOC score

Table 1 Characteristics of participants

Age, mean ± SD (years)	74.0 ± 7.0
Sex (*n*)	
Men	94 (41.0%)
Women	135 (59.0%)
Condition and diagnosis (*n*)	
Normal control	154 (67.2%)
Mild cognitive impairment	53 (23.1%)
Alzheimer's disease	16 (7.0%)
Vascular dementia	4 (1.7%)
Dementia with Lewy bodies	2 (0.9%)
Frontotemporal dementia	1 (0.4%)
Parkinson's disease with dementia	1 (0.4%)
Difficulty in diagnosis	1 (0.4%)
Clinical Dementia Rating (*n*)	
CDR 0	151 (66.0%)
CDR 0.5	54 (23.6%)
CDR 1	9 (3.9%)
CDR 2	7 (3.1%)
CDR 3	8 (3.5%)
Geriatric Depression Scale, mean ± SD	3.6 ± 2.9
Mini-Mental State Examination, mean ± SD	25.9 ± 5.6
Zarit Caregiver Burden Interview, mean ± SD†	2.3 ± 4.7
Personal strain	1.7 ± 3.3
Role strain	0.7 ± 1.9
Score of sense of coherence, mean ± SD	72.4 ± 12.7
Informant about CDR, burden, and SOC (*n*)	
Spouse	151 (65.9%)
Child (living together)	31 (13.5%)
Child (living separately)	27 (11.8%)
Child's partner (living together)	6 (2.6%)
Child's partner (living separately)	3 (1.3%)
Other	11 (4.8%)

†Eight-item version of the test.
CDR, Clinical Dementia Rating; SOC, sense of coherence.

($F_{(3, 75)} = 8.53$, $P < 0.001$) among elderly subjects after controlling for sex and cognitive function.

DISCUSSION

In this study, we aimed to examine the factors that determine caregiver burden and to identify the association between caregiver burden and stress-coping ability. We found that for elderly subjects, caregiver burden was significantly associated with a lower MMSE score of participants and a weakened SOC. Furthermore, SOC was particularly closely related to personal strain in the ZBI after confounding factors such as sex and cognitive function were controlled.

The ZBI score is based on two subscores: personal strain and role strain. Stress-coping ability is related to personal strain, which is 'how personally stressful the experience is'.[29] Reinforcement of SOC might therefore decrease the personal strain of a caregiver's burden. In contrast, role strain, which is 'stress due to role conflict or overload',[29] was not associated with SOC. Therefore, the introduction of formal instrumental support such as respite care would help reduce the role strain of a caregiver's burden rather than enhance stress-coping ability.

To our knowledge, four studies have examined SOC among caregivers for individuals with dementia.[18–20,33] In 2008, Andrén and Elmståhl revealed that caregivers with a lower caregiver burden had significantly higher SOC scores than those with a higher burden. They proposed that a low SOC might be a hallmark characteristic of a high-risk group of caregivers for whom early interventions to reduce the burden would be warranted.[20] Furthermore, Orgeta and Sterzo reported that caregivers with a low SOC are more likely to report high levels of depression and anxiety. They emphasized the need to for psychotherapeutic interventions that target the enhancement of SOC for familial caregivers of people with dementia.[18] In a randomized controlled trial, Langeland *et al.* reported that group talk therapy for community residents with mental health problems enhanced the SOC and life satisfaction of participants.[32] It is therefore expected that employing interventions to enhance SOC, such as the nursing care activities for community residents reported by Langeland *et al.*, might be effective in reducing caregiver burden for dementia. The results of that study, however, pertain to European nations, and there is a paucity of data from research involving Japanese caregivers. The similar association regarding Japanese subjects in the present study lends support to these previous findings.

Our study has several notable limitations. First, cause-and-effect relationships could not be determined because of the cross-sectional study design. Second, only a limited amount of caregiver information was collected, and some potentially confounding factors cannot be ruled out. SOC is believed to be nurtured in the process of maturation. Because it is thought that factors such as familial background, life experience, and individual economic conditions can potentially influence SOC, these caregiver factors should be controlled for in future studies. Third, our analysis did not assess or control for the severity of BPSD. Regarding psychosocial factors of caregivers and the BPSD of participants, these should ideally have been, but were not, controlled for statistically by multivariate data analysis in large samples. Fourth, the paucity of data regarding caregivers for dementia

Table 2 Correlations between age, years of education, cognitive function, sense of coherence, and ZBI

	Age		Years of education		MMSE score		SOC score	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
ZBI score	0.21	0.066	−0.05	0.650	−0.21	0.067	−0.38	<0.001***
Age	–	–	−0.24	0.033*	−0.34	0.002**	−0.14	0.233
Years of education	−0.24	0.033*	–	–	0.17	0.145	0.20	0.076
MMSE score	−0.34	0.002**	0.17	0.145	–	–	−0.16	0.154
SOC score	−0.14	0.233	0.20	0.076	−0.16	0.154	–	–

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. MMSE, Mini-Mental State Examination; SOC, sense of coherence; ZBI, Zarit Caregivers Burden Interview.

Table 3 Association between caregivers' burden and related factors

	β	*t*	*P*-value
Sex (male = 0, female = 1)		n.s	
Age		n.s	
Years of education		n.s	
MMSE score	−0.28	−2.68	0.009**
SOC score	−0.42	−4.10	<0.001***

***$P < 0.001$, **$P < 0.01$. MMSE, Mini-Mental State Examination; n.s means not significance; SOC, sense of coherence.

Table 4 Association between sense of coherence and two subscores of Zarit Burden Interviw

	β	*t*	*P*-value
Sex (male = 0, female = 1)	−0.25	−2.36	0.021*
Age		n.s	
Years of education		n.s	
MMSE score	−0.29	−2.75	0.007**
Zarit Burden Interview			
Personal strain	−0.41	−4.04	<0.001***
Role strain		n.s	

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. MMSE, Mini-Mental State Examination; n.s means not significance.

patients with clinically moderate or severe symptoms may limit the generalizability of results in this study.

In summary, this study yielded new evidence regarding the association between caregiver burden and stress-coping ability. The study's limitations notwithstanding, our findings contribute to a better understanding of the concept of SOC in dementia care. Caregiver burden related to the care of dementia patients is a very common problem in Japan. Therefore, further longitudinal or interventional studies would be worthwhile.

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ORIGINAL ARTICLE

Cancer and non-cancer excess mortality resulting from mixed exposure to polychlorinated biphenyls and polychlorinated dibenzofurans from contaminated rice oil: "*Yusho*"

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Abstract
Purpose In 1968, rice oil contaminated with polychlorinated biphenyls and polychlorinated dibenzofurans caused a severe outbreak of food poisoning in Japan and was termed locally as "*Yusho*" (oil disease). In our previous study, we found that area-based standardized mortality ratios (SMRs) of some diseases were elevated shortly after the incident. This previous study, however, was unable to determine whether these elevated SMRs were a result of other area-specific factors. To overcome this limitation, we obtained mortality data from the 5 years before the incident and conducted an area-based study using vital statistics records dating from 1963 to 2002.
Methods The population of Nagasaki Prefecture was set as the reference population for calculating SMRs. We also included data on cause-specific mortality attributable to cancer and expanded the population to encompass two severely exposed areas where contaminated rice oil was distributed (namely Tamanoura and Naru). We also calculated SMRs in the remainder of the Shimo-Goto region, excluding the exposed area, which was used as a comparison area.
Results Even after considering the time trends in mortality before the incident, mortality due to diabetes mellitus and heart disease, as well as all-cause mortality, was found to be elevated shortly afterward. Additionally, mortalities due to uterine cancer in Tamanoura and leukemia were also elevated at 30–34 and 10–59 years after the event in both exposed areas, respectively. SMRs for leukemia in Tamanoura were as high as 3.0 (95 % confidence interval 1.4–6.2) and 2.4 (1.2–4.8) 10–19 years later. In this period, SMRs for leukemia in the comparison area were not elevated.
Conclusions Further epidemiological studies are needed regarding this rice-oil, "*Yusho*" outbreak, especially with regard to cancer and non-cancer mortality.

Keywords Polychlorinated biphenyls · Chlorinated dibenzofurans · Mortality · Leukemia · Heart disease · Food contamination

Introduction

In 1968, in western Japan, one of the most severe incidents of mass food poisoning in the country occurred and was later referred to as "*Yusho*" (rice-oil disease) (Fig. 1). This incident was reported to have caused a range of health disorders in local residents such as severe acne-like skin lesions, numbness, and other neurological signs (Kuratsune et al. 1972). The source of the outbreak was rice oil intended for culinary use that had been contaminated with polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) (Kuratsune and Masuda 1972; Nagayama et al. 1975).

Although this was one of the most severe incidents of mass food poisoning due to PCBs and PCDFs, epidemiological studies on mortality following the outbreak remain

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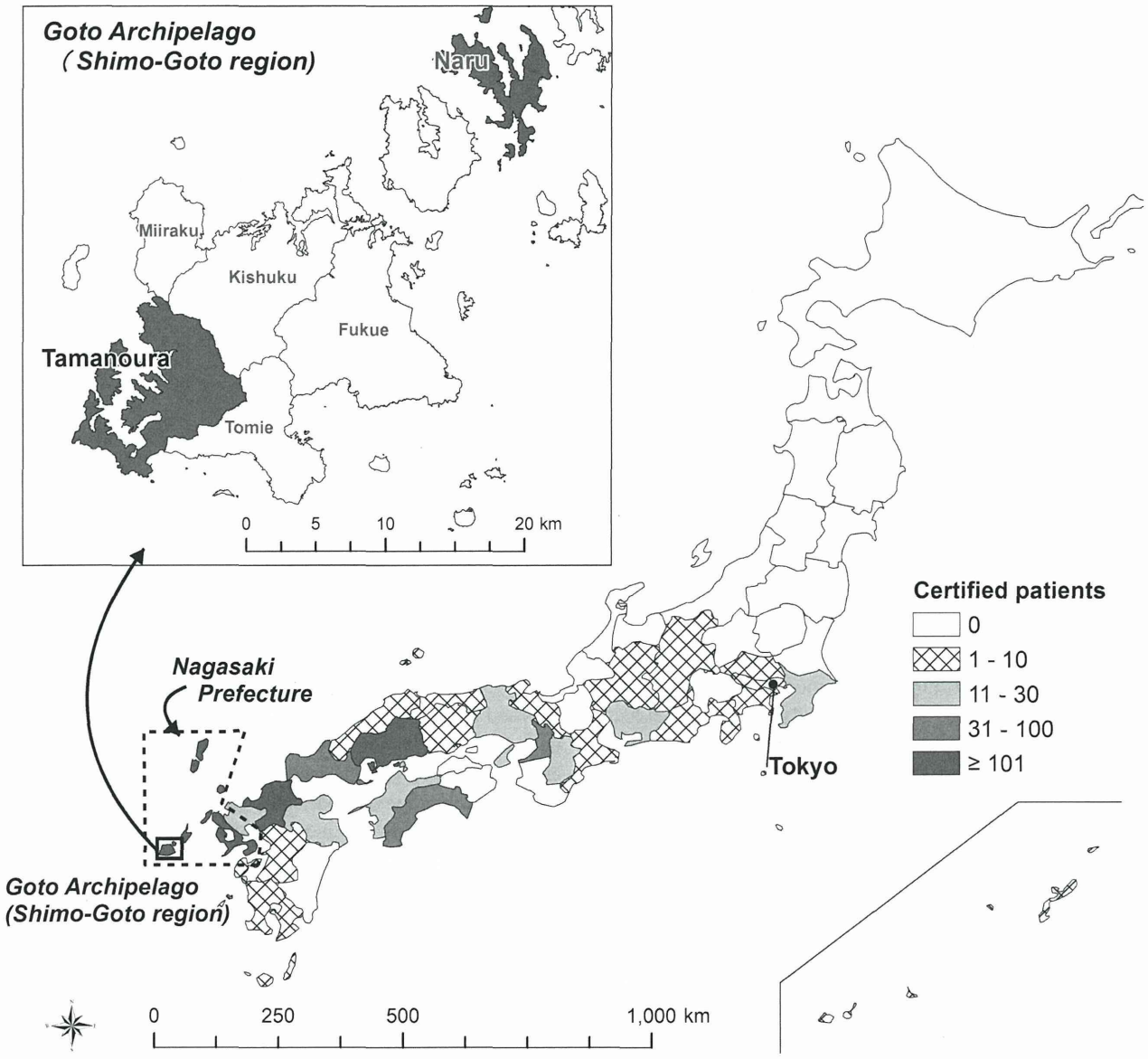

Fig. 1 Distribution map of officially certified Yusho patients in Japan in 1986 and the study area in 2003, including the exposed area (Tamanoura and Naru) and Shimo-Goto region

limited. Indeed, until now, there have been only four epidemiological studies on mortality among officially certified Yusho patients (Ikeda et al. 1987; Ikeda and Yoshimura 1996; Kuratsune et al. 1972; Onozuka et al. 2009), and one ecological study of the exposed area where contaminated rice oil was distributed (Kashima et al. 2011). Although previous studies using cohort data provided some evidence on the effects of contaminated rice oil, they were unable to evaluate the short-term impacts of the outbreak due to their left-censored design (i.e., they could not enroll individuals who died before being officially certifying as Yusho cases). Additionally, especially during its early stage of food poisoning, official certification of Yusho patients was based on a combination of several symptoms with a focus on dermatologic and ophthalmologic findings and a patient's intake of the contaminated rice oil (Kuratsune et al. 1996). Those who did not have the combination of such typical symptoms were not certified even if they had ingested contaminated rice oil or had family members already certified (Shimoda 2008). As a result, these studies, which evaluated only officially certified patients, could not detect an early increase in mortality, especially mortality unrelated to dermatologic findings, in the period immediately following the outbreak. As such, we do not have a comprehensive

Table 1 Sociodemographic characteristics of the exposed, comparison, and reference areas

	Exposed area		Comparison area	Reference area
	Tamanoura	Naru	Shimo-Goto region[a]	Nagasaki Prefecture
Officially certified Yusho patients up to March 2013 [cumulative no. (%)][b]	622 (14.2)	195 (3.0)	0 (0.0)	908 (0.1)
By age group [no. (%)][c]				
0–14 years	1,596 (36.4)	2,383 (36.3)	19,594 (34.0)	439,298 (28.0)
15–59 years	2,057 (46.9)	3,397 (51.7)	29,831 (51.7)	941,102 (59.9)
60+ years	737 (16.8)	789 (12.0)	8,265 (14.3)	189,844 (12.1)
Total	4,390	6,569	57,690	1,570,244
By occupational sector (%)[d]				
Primary (farmers, fishermen, etc.)	48.2	33.2	35.2	23.3
Secondary (factory workers, etc.)	9.4	14.7	14.6	24.9
Tertiary (services, etc.)	12.2	9.1	12.1	13.2

[a] The remainder of Shimo-Goto was analyzed separately from the exposed area (Tamanoura and Naru)

[b] Figures were obtained from Department of Citizens' Life, Nagasaki Prefecture. Percentages were calculated by dividing the number of patients with an officially certified Yusho patients by the total number of residents in each area

[c] Refers to age group in 1970. Source: Nagasaki Prefecture census (1970)

[d] Among workers aged 15 years and above in 1970

understanding of the effects of ingestion of the PCB- and PCDF-contaminated oil.

In our previous ecological study, we evaluated the acute and long-term health effects of ingestion of the contaminated rice oil and focused on the severely affected area (Tamanoura) using data from vital statistics (Kashima et al. 2011). The results indicated that area-based standardized mortality ratios (SMRs) for all causes, including diabetes mellitus, cardiovascular disease, pneumonia/bronchitis, and bronchial/lung cancer, were elevated shortly after the exposure. This previous study, however, did not examine trends in mortality before the outbreak.

To overcome this limitation, we included mortality data from 5 years before the incident and conducted an area-based study to evaluate the acute and long-term health effects arising from mixed exposure to PCBs and PCDFs in contaminated rice oil. The present study was also able to include another exposed area (Naru) in the analyses. Furthermore, we also included more comprehensive data on cause-specific mortality attributable to cancer, including different types of cancer.

Methods

Study areas

Exposed areas (Tamanoura and Naru)

We defined Tamanoura and Naru as the exposed areas (i.e., areas where contaminated rice oil was distributed) (Fig. 1), given that they were severely affected by the outbreak. These towns belong to the Shimo-Goto region, located within the Goto Archipelago in Nagasaki Prefecture (Fig. 1) of Japan. The combined population of the towns was 10,959 in 1970 (4,390 in Tamanoura and 6,569 in Naru, see Table 1). Figure 1 shows the distribution of officially certified Yusho patients obtained from a previous report (Shimoda 2010) based on the *Eleventh Reports of the Study on Yusho and PCB* (Kuratsune et al. 1987). More comprehensive data for the Shimo-Goto region in 2003 were obtained from Nagasaki Prefecture (Nagasaki Prefecture 2013). These data indicate that 622 officially certified cases including 175 deaths in Tamanoura and 195 certified cases including 55 deaths in Naru were reported in the period up to 2013 (Nagasaki Prefecture 2013). This implies that in 1970, approximately at least 14 % of the total population in Tamanoura and 3 % in Naru had sufficient exposure history and clinical signs to be certified as Yusho cases. Because there were 2,210 officially certified Yusho cases as of 2013 (Japanese Ministry of Health 2013), these exposed areas together accounted for around 37 % of all certified cases in Japan. Many people in these areas were accustomed to buying large quantities of rice oil (in 18-l cans or 1.8-l bottles) and sharing it among several families (Japanese Ministry of Health 1972). Additionally, many residents would regularly have lunch or dinner together after fishing in exposed areas. Hence, a large proportion of residents in Tamanoura and Naru were considered to have ingested the contaminated rice oil to some extent, even if they were not certified as Yusho cases.

Table 2 Summary of the condensed list of causes of death corresponding to ICD-7–10

	1963–1967 ICD-7	1968–1978 ICD-8	1979–1994 ICD-9	1995–2002 ICD-10
Non-cancer diseases				
Diabetes mellitus	260	250	250	E10–E14
Heart disease	410–434	393–398, 410–429	393–398, 410–429	I01–I02.0, I05–I09, I20–I25, I27, I30–I52
Hypertensive disease	440–443	400–404	401–405	I10–I13
Cerebrovascular disease	330–334	430–438	430–438	I60–I69
Pneumonia/bronchitis	490–493, 763, 500[a], 501–502	480–486, 490, 491, 466	466.0, 480–486, 490–491	J12–J18[b]
Liver disease	581	571	571	K70–K77
Nephritic disorder	590–594	580–584	584–586	N17–N19
Cancers	140–205	140–209	140–208	C00–C97
Stomach cancer	151	151	151	C16
Bronchial/lung cancer	162, 163	162	162	C32–34
Uterine cancer	171–174	180–182	179–182	C53–C55
Breast cancer	170	174	174–175	C50
Leukemia	204	204–207	204–208	C91–C95

ICD international classification of diseases

[a] Pneumonia/bronchitis in ICD-7 included acute bronchitis (500 of ICD-7)

[b] Only pneumonia was included in this category after the adoption of ICD-10

Reference area (Nagasaki Prefecture)

Since mortality in the Goto Archipelago stratified by age category was not available from the population statistics, we adopted the population of Nagasaki Prefecture as the reference population (Fig. 1), which included residents in both the exposed areas (Tamanoura and Naru) and in other areas, which were home to 91 officially certified cases. Adopting Nagasaki Prefecture as a reference may have resulted in our SMRs being underestimated.

Comparison area (Shimo-Goto region excluding Tamanoura and Naru)

Because both exposed areas are located in the same archipelago (Fig. 1), factors such as lifestyle (e.g., smoking and alcohol consumption), the social and economic environment, and access to medical care and health status among residents may have been different from those in the reference area (Nagasaki Prefecture). The remainder of the Shimo-Goto region excluding Tamanoura and Naru (which included one city and three towns) was therefore selected as a comparison area. To elucidate a geographically local characteristic of SMRs, we additionally estimated SMRs at this comparison area.

Outcome measures

Following previous studies (Kashima et al. 2011; Onozuka et al. 2009), in addition to all-cause mortality, we evaluated mortality due to diabetes mellitus, heart disease, hypertensive disease, cerebrovascular disease, pneumonia/bronchitis, liver disease, all cancers, and bronchial/lung cancer. To evaluate cause-specific mortality in greater detail, deaths due to nephritic disorders and leukemia, as well as cancer of the stomach, uterus and breast, were included among our outcomes. However, owing to a lack of data, we excluded liver cancer from our analysis. We extracted data on non-cancer disease and cancer mortality from vital statistics records in Nagasaki Prefecture from 1963 to 2002. Table 2 shows the causes of death evaluated in the present study with their corresponding International Classification of Disease (ICD) 7–10 codes.

Statistical analysis

To estimate the possible acute and long-term health effects of the contaminated rice oil, we calculated age-adjusted SMRs (Greenland and Rothman 2008) for both cancers and non-cancer diseases in the exposed areas (Tamanoura and Naru) and the comparison area (remainder of Shimo-Goto) from 1963 to 2002. For our analysis, we defined 1963–1967 as the period before the incident and the period starting from 1968 as the period after the incident (Japanese Ministry of Health 1972).

We estimated SMRs for each year from 1963 to 1978 to evaluate the acute effects of the rice oil. We considered the 10-year period following the incident to be the most relevant for determining acute effects, given that the half-lives

of PCDFs and PCBs have been reported to be 5–7 years (Ryan et al. 1993) and approximately 10 years (e.g., PCB 118 from 9.5 to 13.8 years) (Ritter et al. 2011; Seegal et al. 2011), respectively. We estimated SMRs and their 95 % confidence intervals (CIs) in the exposed area (Tamanoura and Naru) and the comparison area (the remainder of the Shimo-Goto region excluding the exposed area) using the population of Nagasaki Prefecture as a reference. We then divided the study period (1963–2002) by 10- and 5-year intervals according to the national census and estimated 10- and 5-year SMRs in both the exposed areas and the comparison area to evaluate long-term effects.

Because the national census is carried out at 5-year intervals in Japan, we assumed the number of people remained the same 2 years before and after the census year in the analyses. We also adjusted SMRs by residents' age according to 5-year age categories.

We estimated the 95 % CI for each SMR using the Wald method and assumed that the number of observed deaths followed a Poisson distribution (Greenland and Rothman 2008). We could not estimate either sex- or age-specific SMRs as we could not obtain data on cancer and non-cancer mortality that were categorized by sex or age in either the exposed area or the comparison area.

Results

Table 1 shows the sociodemographic characteristics of the study areas. While the breakdown of the local population by age and employment by sector in exposed areas (Tamanoura and Naru) was similar to that in the comparison area (Shimo-Goto region), the proportions of the population in the youngest age group and employed in the primary sector were higher in the exposed areas than in the reference population.

The numbers of cases and SMRs for non-cancer diseases in each year from 1963 to 1978 are shown in Table 3. Consistent with our previous findings (Kashima et al. 2011), the SMRs for all causes (after one and 4 years), in addition to diabetes mellitus (1 year), heart disease (accident year to 1 year), and hypertensive disease (4 year) in Tamanoura, were higher in one or several of the first 5 years immediately following the incident when compared with the reference population. While all of these results were statistically significant, there was no consistent increase in SMRs for residents in the comparison area. Among the disease outcomes evaluated, SMRs for diabetes mellitus and heart disease were not higher during the period before the outbreak (1963–1967). Although all-cause mortality was higher at 4 years before the outbreak, SMRs for those diseases were not higher before the outbreak. During the 5- to 10-year period after the outbreak, SMRs for liver disease (SMR: 4.5, 95 % CI 1.7–11.9) and nephritic disorders (SMR: 4.5 95 % CI 1.1–18.0) were significantly higher 10 years after the accident, although they were also elevated before the incident (1963–1967).

Similarly, in Naru, SMRs were found to be elevated for hypertensive disease after 4 years (SMR: 2.9, 95 % CI 1.3–6.4), for pneumonia and bronchitis after 5 years (SMR: 2.9, 95 % CI 1.4–6.0), 6 years (SMR: 2.4, 95 % CI 1.1–5.0), and 10 years (SMR: 4.2, 95 % CI 2.3–7.6), and nephritic disorders after 1 year (SMR: 3.3, 95 % CI 1.1–10.3). Additionally, nephritic disorders were not found to have been elevated during the period leading up to the outbreak (1963–1967).

Furthermore, the combined SMRs for non-cancer disease at the whole exposed areas (Tamanoura & Naru) in each year are shown in Online Table 1. Combined SMRs for all causes (after 4 years), diabetes mellitus (1 and 9 years), hypertensive disease (4 years), pneumonia, bronchitis (5, 6, and 10 years), and nephritic disorder (6 and 10 years) were also elevated at the whole exposed areas. On the other hand, a significant elevation for combined SMRs for heart disease was not observed.

Table 4 shows the number of cases and pooled SMRs for non-cancer disease during the whole period before the accident (1963–1937) and after the period (1968–1978) in the exposed area and Shimo-Goto region. Regarding the pooled SMRs for the period after the accident over 10 years, although the all-causes and diabetes mellitus mortality in Tamanoura were elevated at borderline significant, significant SMRs were not observed at both Tamanoura and Naru. The combined SMRs for non-cancer disease at the whole exposed area (Tamanoura & Naru) during the whole period for the period before and after the accident are shown in Online Table 2.

Table 5 shows the number of cases and SMRs for cancer from 1963 to 2002 at 10-year intervals. In Tamanoura and Naru, the SMR for all-cancer mortality was elevated at 30–34 years, but the SMR in the Shimo-Goto region during the period was also elevated. Additionally, in Tamanoura, the SMR for uterine cancer was 4.1 times higher (95 % CI 1.3–12.6) than that in the reference population after 30–34 years, while the SMR for leukemia was 3.0 times higher after 10–19 years (95 % CI 1.4–6.2). Finally, in Naru, SMRs for leukemia were significantly higher than those of the reference population after a 10- to 34-year period following the incident. While SMRs of leukemia in the Shimo-Goto region were also elevated after 20 years, elevated SMRs were not observed at a period of 10–19 years. The SMRs for all cancer, uterine cancer, and leukemia were not elevated in the period before the accident. The combined SMRs for cancer mortality at the whole exposed area (Tamanoura & Naru) at 10-year intervals are shown in Online Table 3. All-cancer mortality (30–34 years), uterine