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# UNCOVERING GEOGRAPHIC CONCENTRATIONS OF ELEVATED MESOTHELIOMA RISKS ACROSS JAPAN: SPATIAL EPIDEMIOLOGICAL MAPPING OF THE ASBESTOS-RELATED DISEASE

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*Abstract* Disease mapping is an effective analytical approach to conducting epidemiological analysis as well as risk communications to share fundamental knowledge of existing/emerging epidemics. This article employs a series of spatial epidemiological techniques for enhanced disease mapping of the mesothelioma epidemic at the municipality level across Japan during the period between 1995 and 2004. The processing of data using spatial statistics is vital in the effective geovisualisation. The results revealed distinctive geographical concentrations of highly elevated mesothelioma risks, especially in areas with a history of prior asbestos-related manufacturing industries, such as textile, construction materials and shipbuilding factories.

**Key words:** asbestos-related diseases, disease mapping, empirical Bayes smoothing, excess deaths, spatial scan statistics, cartogram, pleural mesothelioma, geographic information system

## 1. Introduction

Mesothelioma is representative of asbestos-related diseases, due to its strong causal link with past asbestos exposure. Recently, the incidence of the disease has been steadily and rapidly increasing in Japan (Fig. 1). However, since the national cancer registry system has not yet been implemented, details of the disease epidemic are still not fully known. The death count caused by pleural mesothelioma only began to be recorded in 1995 when ICD-10 was introduced for classifying primary cause of death in Japanese vital statistics. The total number of deaths caused by mesothelioma from 1995 to 2012 was 16,235 (male: 12,671; female: 3,564). Asbestos is now acknowledged to be the leading source of occupational respiratory cancers in Japan (Morinaga *et al*. 2001). Considering the delay in imposing the ban on asbestos use (fully banned in 2002), and the long latency period of the disease (over 30 years), we expect the rising trend in the number of mesothelioma deaths to continue for the next several decades.

The geographical distribution of mesothelioma is one of the key factors in comprehending this asbestos-related disease epidemic. This information may integrate our existing partial knowledge of the link between past exposure and emerging victims (i.e., disease cases), while also providing a means for detecting unrecognised risks of asbestos-related diseases. In 1995, a local newspaper

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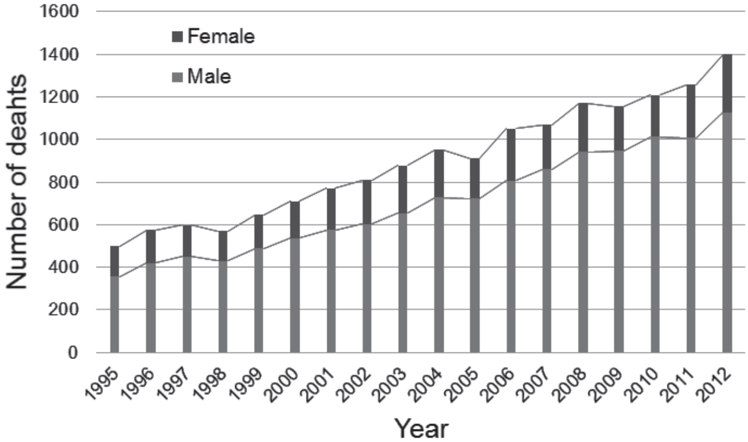


**Fig. 1** The temporal trend of deaths from mesothelioma in Japan, 1995–2012. Source: Vital Statistics in Japan (Ministry of Health, Labour and Welfare)

reported five mesothelioma cases without a history of occupational asbestos exposure in the vicinity of a former asbestos cement pipe plant of Kubota Corporation (hereafter, Kubota plant) in Amagasaki city. These cases raised a serious concern about exposure to airborne asbestos emitted revealing a striking mapping result indicating a clear geographic concentration around the Kubota from the Kubota plant. Soon after, Kurumatani and Kumagai (2008) confirmed the link by plant; they did so by spotting past residences of mesothelioma cases that did not have any history of occupational exposure.

This seminal mapping study shared several features with the legendary work of John Snow on the mapping of cholera in the 19th century (Snow, 1855). Snow mapped the residential locations of cholera deaths to confirm the use of a water pump as the most plausible putative source of contaminated water. However, such spot mapping efforts have been conducted mainly for investigating specific putative sources of contamination of asbestos in small geographic areas, and are not appropriate for revealing a wider geographic context of the current mesothelioma epidemic in Japan. This short article thus aims to examine the geographic variations in mesothelioma mortality throughout Japan by visualising the geographic concentrations of elevated mesothelioma risks at the municipal level. We also demonstrate how geovisualisation of mesothelioma risks is enhanced by spatial epidemiology techniques in a geographic information system (GIS) environment (Nakaya 2008; Pfeiffer *et al*. 2008).

Although the regional mortality from mesothelioma according to vital statistics is usually available only at the level of 47 prefectures, the geographic list of mesothelioma death counts (only sex combined information) from 1995 to 2004 at the municipality level (*Shi-cho-son*) was included in a reference table in meeting records from the Ministry of the Environment. If the number of deaths in a region ranges from one to three, the regional count is masked in the list. The masked integer values were restored by maximizing the Poisson likelihood, assuming the relative risk for the masked regions as a constant for each prefecture. Using this death count data source, we prepared the dataset of standard mortality ratio (SMR) with regional age- and sex-specific population sizes obtained from the 2000 population census for our disease mapping efforts. The number of municipality in the dataset is 1,837.

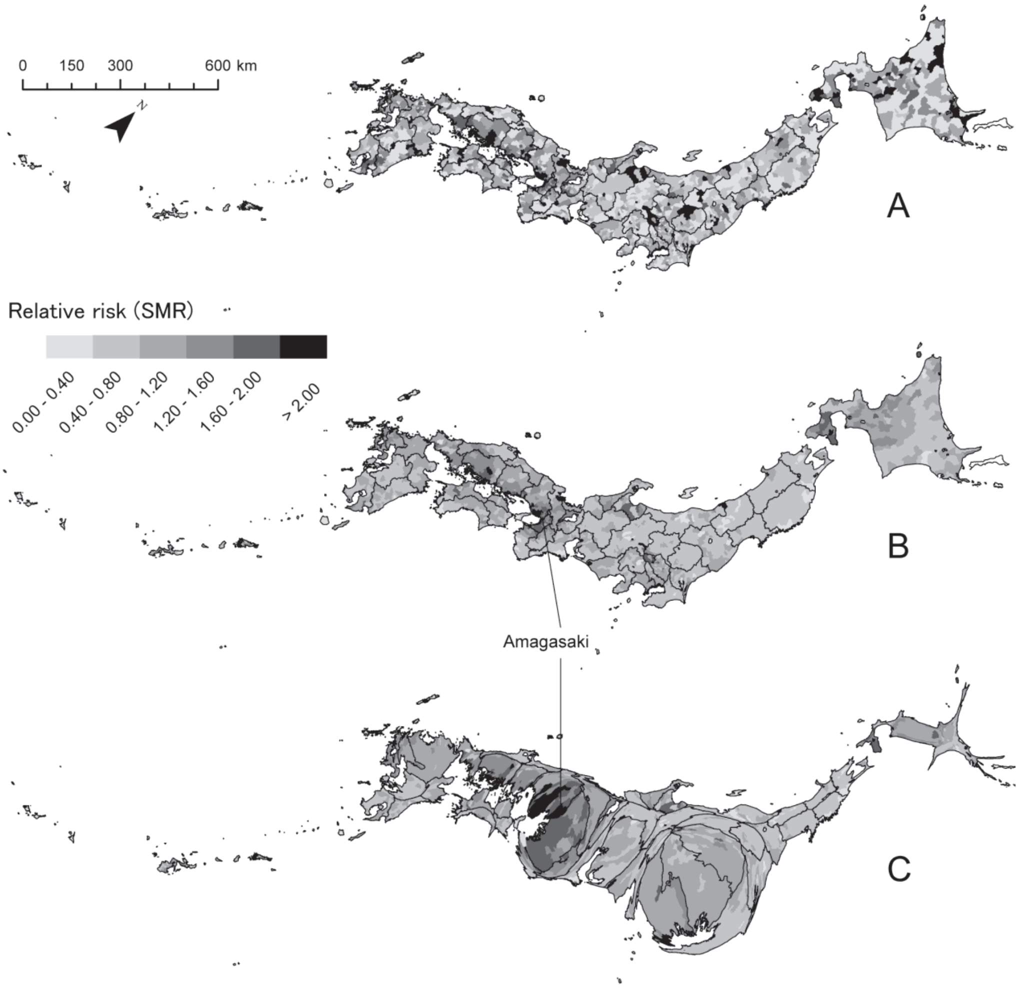


**Fig. 2** Standard mortality ratio (SMR) distribution of mesothelioma, 1995–2004.
A: raw SMR, B: smoothed SMR using spatial empirical Bayes estimates,
C: smoothed SMR based on the population cartogram

## 2. Spatially Smoothed Mapping of Mesothelioma Mortality

Kanazawa *et al*. (2006) mapped the standard incidence ratio (SIR) of mesothelioma within Osaka prefecture at the municipal level, indicating an uneven mesothelioma incidence distribution. This study would be the first trial mapping the regional distributions of mesothelioma incidence on the basis of long-term cancer registration data, revealing remarkable small-area variations within a prefecture. However, since a small number of asbestos-related cancer cases leads to an inaccurate estimate of SIR, we should carefully consider such thematic maps at the level of small areal aggregation units. It is important to recognize that rural regions with a low population density tend to be large; therefore, unreliable SIR estimates in such rural regions would obscure the geographic tendency. The small-number problem occurs with the mapping of the distribution of nationwide mesothelioma SMR distribution in Japan (Fig. 2A). Thus, it is difficult to infer the meaningful geographical trends or concentrations of high mesothelioma SMRs in the thematic map.

To overcome the difficulties in disease mapping using low death counts, various statistical and cartographical approaches have been developed in the field of spatial epidemiology. Spatial smoothing is commonly employed as the first step to stabilize statistically unreliable regional rate estimates such as SIR or SMR. Empirical and full Bayesian models with spatial dependency have been widely employed for this purpose (Lawson 2013).

Figure 2B shows the result of applying spatial empirical Bayes smoothing (Marshall 1991) to the SMR data set of mesothelioma cases studied from 1995 to 2004. The regional relative risk estimate, which is calculated using this statistical technique, shrinks to the average SMR in the neighbourhood of a region if the number of expected cases in the region is small. However, the relative risk estimates are not largely different from the raw SMR for populous regions with a large number of expected cases. A spatial empirical Bayes estimator of SMR in the $i$th region, $SMR_i^{EB}$, is expressed as

$$SMR_i^{EB} = \frac{o_i + \beta_{(i)}}{e_i + \alpha_{(i)}}$$

where $o_i$ and $e_i$ are the number of observed and expected cases, and $\alpha_{(i)}$ and $\beta_{(i)}$ are positive hyperparameters estimated from the regionally pooled data in the neighbourhood of region $i$. It should be noted that $\beta_{(i)} / \alpha_{(i)}$ corresponds to the SMR in the pooled data. Neighbourhoods are defined using a moving window by defining a second order queen contiguity weighting matrix for each region. The result indicates that the western part of Japan along the Seto Inland Sea has experienced higher mortality due to mesothelioma.

### 3. Highlighting Geographical Regions with Excess Deaths from Mesothelioma

In Figure 2C, the smoothed SMR is mapped on a population cartogram in which the size of each spatial unit is proportional to the population size (here, the number of expected cases is used as the base population). In the cartogram, values in populous areas become visually dominant. We used the algorithm developed by Gaster and Newman (2004) to construct continuous cartograms. This method of mapping enables us to understand a geographical trend in high-risk areas observed in western Japan, particularly, the locally increased risk in conurbations along the Seto Inland Sea. In such locations, municipalities are likely to be populous but geographically small, such that we visually overlook the importance of local excess deaths on a standard map projection. In fact, we cannot identify Amagasaki city as having one of the highest SMRs on the standard map projection with the equidistant conic projection centred in Tokyo (Fig. 2B).

Combining the cartographic visualisation of excess deaths with 3D visualisation provides a bird's eye view of the cartogram-based excess death distribution; that is, a more direct visualisation of the geographical distribution of excess deaths (Nakaya 2010). Figure 3 shows the prismatic display of SMR distribution based on the cartogram in which the height of each municipality is proportional to its SMR. Given that the areal size and height of a geographic unit represent the regional population (number of expected cases) and regional SMRs (relative risks of death), respectively, the volume of "mountains/prism," (areal size multiplied by the height) shown on the 3D map corresponds to the absolute size of excess deaths, compared with cases with no history of asbestos exposure. We observe several considerably large volumes of excess deaths, particularly in and around Amagasaki city and other cities with shipbuilding (such as Aioi, Kobe, Tamano, and Kudamatsu), seaports with naval bases (Kure, Maizuru, and Yokosuka), and asbestos-related manufactguring industries (such as Amagasaki, Hashima, Sennan, and Ohji).

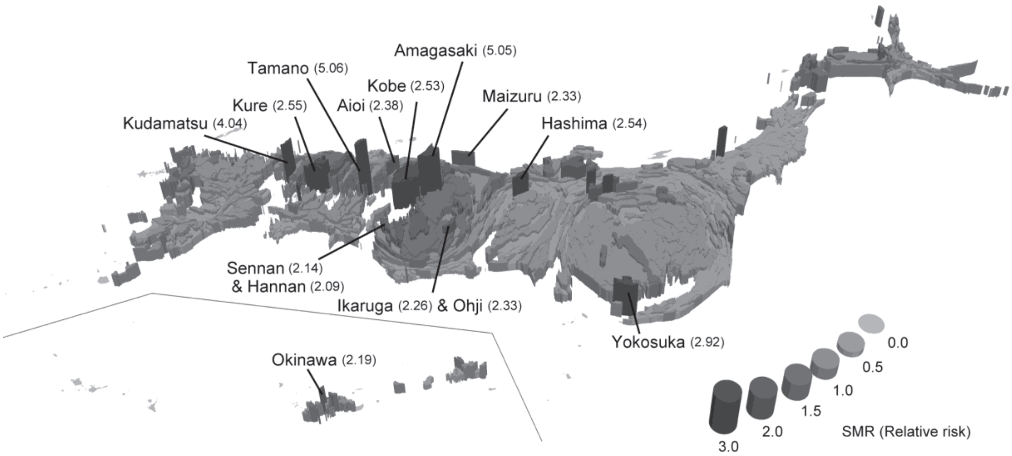


**Fig. 3** Prismatic display of excess deaths from mesothelioma in Japan, 1995–2004. The colour and height represents SMR (spatial empirical Bayes estimates of relative risk). Numbers in parenthesises refer to the regional SMRs.

## 4. Detecting Spatial Clusters of High Mesothelioma Risks

Considering the fact that a geographic unit is modifiable, we should carefully take into account the zone design for the geographical spatial analysis. The significance testing of SMR levels on the basis of the Poisson probability is often conducted for each basic geographic unit. However, the statistical power is dependent on the number of expected cases. Thus, in the case that regional excess deaths are insignificant at the level of the basic unit, the results might be different at the level of larger aggregated units. Further, the classic Poisson test suffers from multiple-testing problems because it repeats the local evaluations of anomalous values countless times. It should be noted that although geographical smoothing using the spatial empirical Bayes estimator generally provides conservative estimates, spurious geographic patterns of estimated relative risks can still emerge depending on the local geographic settings. Thus, it is necessary to use a more stringent test to assess whether a geographically elevated risk is significantly high.

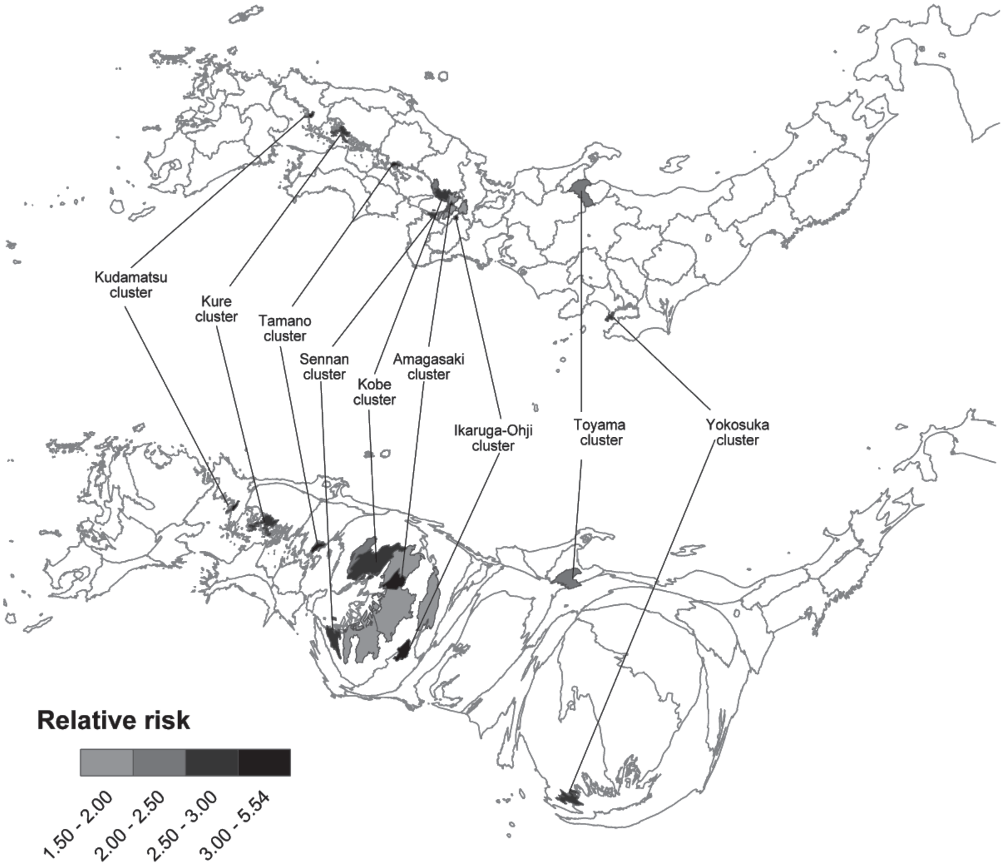


**Fig. 4** Statistically significant clusters of elevated risks of mesothelioma detected using spatial scan statistics ($p$ values <0.05).

Spatial scan statistics are devised to detect significant clusters by exhaustively scanning the space using moving circular windows with different radii (Kulldorff 1997). The scan statistics provide a way to avoid performing multiple tests by focusing on the maximum value in the entire study domain. The method is now commonly applied to spatial statistics for various purposes regarding spatial cluster detection.

The test statistic is the observed maximum likelihood ratio in a circular window in the entire geographic domain under study. Omitting a constant term, the statistic is given as

$$\lambda = \sup_{Z} \left( \frac{y(z)}{e(z)} \right)^{y(Z)} \left( \frac{y(z^c)}{e(z^c)} \right)^{y(Z^c)} I\left( \frac{y(z)}{e(z)} > \frac{y(z^c)}{e(z^c)} \right),$$

where $y$ and $e$ denote the number of observed and expected cases, respectively; $Z$ and $Z^c$ represent domains inside and outside the specified window, respectively; and $I$ is the indicator function (if $a$

$> b$, then I ($a > b$) becomes 1, otherwise 0).

Under the null assumption that the disease cases under study randomly occur following a Poisson distribution with expected size of death as its mean, Monte Carlo replications of the dataset enable us to obtain the simulated distribution of the likelihood ratio-based statistics, $\lambda$, for the significance testing of high-density clusters. We generated 999 replications to obtain *p*-values, the probability of random occurrence of observed excess deaths in a circular window. The cluster defined by the window with the lowest *p*-value is called the most likely cluster. Secondary clusters are also obtained for those that do not geographically overlap more likely clusters if their *p*-values are below the significance level.

Selecting the upper geographical search limit for scan statistics is crucial, because it is well known that if the upper limit is set to a large value, the spatial scan statistics are likely to generate a few extra-large and low-risk clusters (Pfeiffer *et al*. 2008). We herewith use a radius of 10 km as the upper search limit to confirm the regional, citywide geographic concentrations of excess deaths. Distances are calculated as the crow-fly distance between municipality centroids. Figure 4 shows statistically significant concentrations of high relative risks detected by using spatial scan statistics at the 5% significance level. Even if we exclude the originally masked data from the dataset, the result is essentially unchanged.

The detected clusters again highlighted the regions with navy ports, shipbuilding, textile, or other manufacturing industries that used asbestos. These clusters are mainly distributed in western Japan. The figure also shows an unidentified local cluster in the city of Toyama, confirming the occurrence of anomalous excess deaths visualised in the thematic map of SMR (obtained by conservative statistical testing).

## 4. Discussion

As demonstrated by the seminal work of Kurumatani and Kumagai (2008), unidentified risks, including hidden sources of asbestos exposure or unknown putative sources, can be explored and confirmed by adopting a disease mapping approach. The visualisation of the regional distribution of mesothelioma incidence in a wider geographic context is also well powered by mapping, spatial statistics, and the GIS-related cartographical analysis such as cartograms. We assessed the extent of the epidemic by directly visualising the number of excess deaths estimated by using empirical Bayesian smoothing on the basis of a population cartogram in 2D or 3D GIS environments. Spatial scan statistics provide a method for the conservative testing of local geographical concentrations of mesothelioma deaths. It is well documented that the geographic concentrations of mesothelioma deaths in areas with seaports support the fact that heavy occupational exposure to asbestos occurred in old shipbuilding workplaces in many countries, including the U.K. and U.S. (Jenal *et al*. 2000). Our disease mapping efforts reveal similar geographic concentrations of mesothelioma deaths, indicating heavy past exposure to asbestos due to the presence of asbestos-related manufacturing industries, including shipbuilding factories. It suggested that occupational exposures to asbestos in closed working environments was the main cause of mesothelioma geographic clusters except Amagasaki city where neighbourhood exposures to asbestos emitted from a factory led to one of the largest concentrations of mesothelioma deaths We also found some unrecognized geographic clusters that need to be explored further (such as Toyama). It is worth noting that uncovering such unrecognised geographic concentrations of mesothelioma be crucial for comprehending the entire picture of mesothelioma epidemic and making social policies to fully cover the associated victims.

An important issue for future research is the inclusion of temporal dimensions to predict the future geographic trend of asbestos-related diseases. In the U.K., wherein the epidemic started earlier than in Japan, there remain geographic concentrations of excess deaths in ports and dockyards, but the rate of increase in the number of excess deaths has reduced, because of the migration of previously exposed people from high-risk to low-risk areas (Health and Safety Executives 2005). This implies that excess deaths would be underestimated by the current SMRs in such high-risk areas. The study conducted in the U.K. also suggests that while the number of excess deaths due to heavy exposure has been declining, the incidence of asbestos-related disease continues to increase among those working at construction industries that are widely distributed across regions. Thus, it is essential to contextualize the information regarding an epidemic according to the changing geography; that is, in terms of population composition, occupational exposure, migration history, and resources supporting those at risk. We should further explore the ways in which GIS facilitates contextualization as an information platform by visualising and linking different information over space and time.

## Acknowledgements

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## References

Gastner, M.T. and Newman, M.E.J. 2004. Diffusion-based method for producing density equalizing maps. *Proceedings of the National Academy of Sciences* **101**: 7499–7504.

Health and Safety Executives 2005. *Mesothelioma Mortality in Great Britain: Analyses by Geographical Area and Occupation 2005*. National Statistics of the UK.

Jenal, A., Grauman, D. and Devesa, S. 2000. Recent geographic patterns of lung cancer and mesothelioma mortality rates in 49 shipyard counties in the United States, 1970–94. *American Journal of Industrial Medicine* **37**: 512–521.

Kanazawa, N., Ioka, A., Tsukuma, H., Ajiki, W. and Oshima, A. 2006. Incidence and survival of mesothelioma in Osaka, Japan. *Japanese Journal of Clinical Oncology* **36**: 254–257.

Kulldorff, M. 1997. A spatial scan statistic. *Communications in Statistics – Theory and Methods* **26**: 1481–1496

Kurumatani, N. and Kumagai, S. 2008. Mapping the risk of mesothelioma due to neighborhood asbestos exposure. *American Journal of Respiratory and Critical Care Medicine* **178**: 624–629.

Lawson, A.B. 2013. *Bayesian disease mapping: hierarchical modeling in spatial epidemiology. Second Edition.* Boca Raton: CRC Press.

Marshall, R.J. 1991. Mapping disease and mortality rates using empirical Bayes estimators. *Applied Statistics* **40**: 283–294.

Morinaga, K., Kishimoto, T., Sakatani, M., Akira, M., Yokoyama, K. and Sera, Y. 2001. Asbestos-related lung cancer and mesothelioma in Japan. *Industrial Health* **39**: 65–74.

Nakaya, T. 2008. Spatial epidemiology in geographic information system environments, *Journal of the National Institute of Public Health* **57**: 99–116.*

Nakaya, T. 2010. 'Geo-morphology' of population health in Japan: Looking through the cartogram lens. *Environment and Planning A* **42**: 2807–2808.

Pfeiffer, D.U., Robinson, T.P., Stevenson, M., Stevens, K.B., Rogers, D.J. and Clements, A.C.A. 2008. *Spatial Analysis in Epidemiology*. Oxford: Oxford University Press.

Snow, J. 1855. *On the mode of communication of cholera. 2nd ed*. London: J. Churchill. Reprinted in *Snow on Cholera*. New York: The Commonwealth Fund, 1936.

(*: in Japanese with English abstract)