RESEARCH ARTICLE

Breast Cancer Clustering in Kanagawa, Japan: A Geographic Analysis

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Abstract

Background: The purpose of the present study was to determine geographic clustering of breast cancer incidence in Kanagawa Prefecture, using cancer registry data. The study also aimed at examining the association between socio-economic factors and any identified cluster. Materials and Methods: Incidence data were collected for women who were first diagnosed with breast cancer during the period from January to December 2006 in Kanagawa. The data consisted of 2,326 incidence cases extracted from the total of 34,323 Kanagawa Cancer Registration data issued in 2011. To adjust for differences in age distribution, the standardized mortality ratio (SMR) and the standardized incidence ratio (SIR) of breast cancer were calculated for each of 56 municipalities (e.g., city, special ward, town, and village) in Kanagawa by an indirect method using Kanagawa female population data. Spatial scan statistics were used to detect any area of elevated risk as a cluster for breast cancer deaths and/or incidences. The Student t-test was performed to examine differences in socio-economic variables, viz, persons per household, total fertility rate, age at first marriage for women, and marriage rate, between cluster and other regions. Results: There was a statistically significant cluster of breast cancer incidence (p=0.001) composed of 11 municipalities in southeastern area of Kanagawa Prefecture, whose SIR was 35 percent higher than that of the remainder of Kanagawa Prefecture. In this cluster, average value of age at first-marriage for women was significantly higher than in the rest of Kanagawa (p=0.017). No statistically significant clusters of breast cancer deaths were detected (p=0.53). Conclusions: There was a statistically significant cluster of high breast cancer incidence in southeastern area of Kanagawa Prefecture. It was suggested that the cluster region was related to the tendency to marry later. This study methodology will be helpful in the analysis of geographical disparities in cancer deaths and incidence.

Keywords: Breast cancer - cancer registry data - regional clustering - spatial epidemiology

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Introduction

In the past, cancer control and prevention in Japan have been organized according to 47 Prefectures. Therefore, cancer data are often evaluated at the level of the prefectural unit. It has long been known that there is a regional disparity in cancer mortality (Kuroiwa et al., 2004). Such regional disparities were shown to be prominent in gastric, liver, breast cancer, and leukemia and age-adjusted cancer mortality under age 75 years old (Sobue et al., 2012). Among women in Japan, breast cancer mortality is higher in metropolitan regions such as Tokyo, as well as in Kanagawa and Saitama Prefectures in eastern Japan. Detailed observations have indicated a secular change in regional disparities in mortality (Cancer Statistics Editorial Committee, 2010); these reports suggest that breast cancer is sometimes concentrated in a specific region. However, cancer data reflecting any differences that may exist between the urban regions, rural regions, and fishing villages of the same prefecture may be 'averaged out' when the data are evaluated at the level of the prefectural unit. Such averaging could result in a failure to clearly depict real regional disparities. (Meng et al., 2005).

In light of these circumstances, attempts have been made to monitor cancer-related data on the basis of smaller region units, e.g., counties in the United States (Hoover et al., 1975); and cities, counties, and regional meshes in Japan (Ookubo et al., 1977; Fukuda et al., 2005; Nakaya, 2011). Monitoring on the basis of smaller region units enables more detailed examinations of the incidences of diseases, as well as mortalities, and enables more accurate identification of the regions that require increased efforts regarding prevention, including early detection and early

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treatment. To formulate effective measures for cancer prevention and control, especially regarding cancers with high survival rates, such as breast cancer, both mortality and incidence data need to be taken into consideration when determining the optimal focus for such measures.

It would therefore be useful to clarify the map with geographical distribution of cancer incidence and mortality. In recent years, increasing attention has been given to an academic field called spatial epidemiology (Kulldorff. 1997). This is an academic discipline that aims *i*) to describe geographical variations in the occurrence of symptoms representing health risks, diseases, and deaths, *ii*) to consider geographical variations in risk factors such as demographical, environmental, and socio-economic status (SES), *iii*) to detect systematic and non-random changes and differences in geographical factors underlying diseases, and *iv*) to carry out factor analysis (Tango et al., 2007).

One tool that has been effectively used for this purpose is the disease map, which can take the form of a "point data map" or a "counting data map". Counting data maps usually display either relative rates in each region, as measured by a standardized mortality ratio (SMR) or age-adjusted mortality rate or some similar index. In addition, increasing attention has been paid to spatial epidemiology, largely due to the establishment of statistical methods for analyzing spatial information relevant to diseases and due to the availability of geographical information concerning risk factors (Tango et al., 2007).

Previous studies using geographic analysis have demonstrated regional clustering of breast cancer only for mortality data. (Kulldorff et al., 1997, Doi et al., 2010).

The purpose of this study is to investigate whether there are clusters or breast cancer deaths or clusters of breast cancer incidence of statistical significance in Kanagawa Prefecture. SMR or SIR values are unstable in regions with particularly small populations, rendering them unsuited for regional comparison with other municipalities of different population sizes (Tango, 2000). In this study attempted identified high mortality and incidence region of breast cancer using spatial scan method.

The study also aimed at examining the association between socio-economic factors and identified clustering regions.

Materials and Methods

Data collection

Kanagawa Prefecture, Japan is located in the southwest of the Kanto region and south of Tokyo (Figure 1). In 2010, the population of Kanagawa Prefecture was 9,048,331 people, second only to Tokyo. To compile incidence data abstract from the Kanagawa population-based cancer registry, we used data for women diagnosed with breast cancer for the first time from January to December 2006. The data consisted of 2,326 incidences were extracted from a total of 34,323 incidences, including gender, age and residential address (Kanagawa Prefecture, Health and Welfare Division 2011). We also extracted the number of observed deaths due to breast cancer from data regarding 794 deaths, including gender, age,

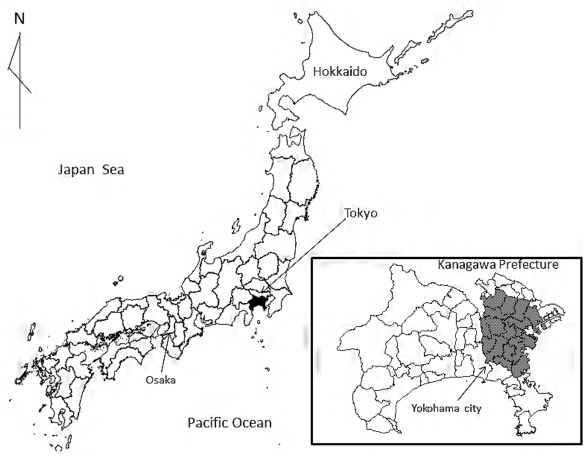

Figure 1. Kanagawa Prefecture in Japan

and simplified classification of cause of death, from the Population Survey Report statistical archives chapter each city, district, town, and village in Kanagawa Prefecture (Statistical Yearbook of Kanagawa Prefectural Public Health, 2006).

Population figures were based on Kanagawa Prefecture's women population (Ministry of Internal Affairs and Communications, Bureau of Statistics, Population census 2005). Subjects were divided into three age groups, viz 0–14, 15–64, and 65 years and over. To obtain SMR for each age group, expected mortality was calculated by multiplying the determined mortality rates by the populations of the corresponding groups in each of 56 municipalities (e.g., city, town, or village) respectively. SMR was then expressed as a ratio of the expected mortality to the corresponding number of deaths encountered in each municipality. Similarly, SIR was calculated from the incidence data from the regional cancer registry (Table 1). All the analyses were based on 56 municipalities (e.g., cities, special wards, towns, and villages) in Kanagawa Prefecture.

SMR and SIR were then plotted on the map for each municipality in Kanagawa Prefecture. To draw this map, latitude and longitude data of municipalities of Kanagawa Prefecture were collected from the location information handbook for municipalities issued by the Japan Map Center of the Geographical Survey Institute of Japan (Japan Map Center, 2009). The points used as coordinates for municipalities were the locations of the offices of the respective municipal governmental bodies using Mapinfo Professional version 11.0 (Pitney Bowes Software K.K).

The variables of persons per household, total fertility rate, and age at first-marriage for women, and marriage rate were taken from the vital statistics (Kanagawa Prefecture, Bureau of Health Welfare 2006).

Statistical analysis

A disease cluster is defined as a geographically bounded group of occurrences of sufficient size and concentration to be unlikely to have occurred by chance without any assumptions about the shape or form of the cluster. To identify the disease clusters and their approximate location, we used a flexible spatial scan statistic with are restricted likelihood ratio (Tango and

Table 1. Breast Cancer SMR and SIR in Kanagawa Prefecture (2006) and Population Density, total Fertility rate, persons per Households, first Marriage Age of Women, Marriage rate and Mortality.

City (County)	Ward	Town	SMR**	SIR**	Population density* person/km²	Persons per households	Total fertility rate	First marriage age of women	Marriage rate	Mortality (death number)
Yokohama	Tsurumi-ku		1.20	1.54	7,991	2.25	1.30	28.2	7.8	28
	Kanagawa-ku		1.10	1.91	9,249	2.11	1.08	28.2	7.4	21
	Nishi-Ku		0.80	2.52	12,160	2.01	1.01	28.6	8.0	6
	Naka-Ku		1.60	2.47	6,780	1.97	1.05	28.4	7.7	20
	Minami-Ku		1.00	2.96	15,560	2.20	1.03	28.2	6.6	19
	Hodogaya-Ku		0.90	2.40	11,125	2.56	1.06	28.1	5.4	16
	Isogo-Ku		1.20	2.94	9,329	2.37	1.18	28.1	6.0	18
	Kanazawa-Ku		1.00	2.89	7,563	2.56	1.20	28.1	5.0	19
	Kouhoku-Ku		0.90	1.59	8,482	2.37	1.16	28.7	8.2	25
	Totsuka-Ku		1.00	1.70	6,852	2.49	1.34	28.1	6.4	24
	Kounan-Ku		1.30	2.83	10,115	2.19	1.18	28.2	5.4	26
	Asahi-Ku		1.00	2.55	6,756	2.55	1.18	27.9	5.4	23
	Midori-Ku		0.90	1.86	8,490	2.58	1.32	28.1	6.3	13
	Seya-Ku		1.00	2.82	6,547	2.71	1.34	27.9	6.1	12
	Sakae-Ku		1.30	2.96	7,480	2.56	1.23	28.0	5.5	15
	Izumi-Ku		1.50	2.67	6,729	2.55	1.29	28.1	5.5	20
	Aoba-Ku		0.70	1.52	6,493	2.72	1.20	28.4	6.2	17
	Tuzuki-Ku		0.80	1.30	7,449	2.62	1.33	28.3	5.7	11
Kawasaki	Kawasaki-Ku		1.60	1.09	5,245	2.14	1.32	27.6	7.8	28
	Saiwai-Ku		1.40	1.06	14,418	2.26	1.32	28.3	7.7	18
	Nakahara-Ku		0.90	1.73	14,546	2.03	1.12	28.9	10.2	16
	Takatsu-Ku		0.50	1.15	12,540	2.19	1.21	28.6	8.6	9
	Tama-Ku		1.10	1.28	11,243	2.44	1.10	28.9	8.3	19
	Miyamae-Ku		0.90	1.23	10,061	2.10	1.24	28.3	7.4	16
	Asao-Ku		0.90	1.30	6,758	2.44	1.17	28.7	5.9	13
Yokosuka			1.20	2.67	4,203	2.62	1.26	27.5	5.5	47
Hiratsuka			0.90	2.61	3,831	2.56	1.29	27.5	5.9	21
Kamakura			1.00	1.62	4,364	2.45	1.10	28.7	5.6	18
Hujisawa			0.90	2.28	5,733	2.43	1.21	28.1	6.2	33
Odawara			0.70	1.19	1,744	2.63	1.21	27.7	5.8	14
Chigasaki			1.10	2.21	6,409	2.56	1.20	28.0	6.0	23
Zushi			0.70	3.03	3,368	2.49	1.14	29.2	4.9	4
Sagamihara			0.90	1.81	2,745	2.43	1.17	27.7	6.2	54
Miura			2.40	2.01	1,538	2.78	1.08	26.8	3.9	12
Hadano			0.70	1.17	1,627	2.52	1.12	27.3	5.1	10
Atsugi			1.00	2.54	2,386	2.46	1.24	27.4	6.3	18
Yamato			1.30	2.61	8,218	2.40	1.24	28.0	7.7	24
Isehara			1.20	1.69	1,812	2.50	1.25	27.7	6.6	10
Ebina			1.00	2.35	4,703	2.61	1.23	28.1	6.5	10
Zama			0.30	2.49	7,263	2.46	1.28	27.7	6.5	3
Minami-ashigara			1.50	1.12	574	2.89	1.31	27.1	5.6	6
Ayase			0.70	2.79	3,670	2.70	1.27	26.9	6.1	5
Miura-county		Hayama	1.80	3.88	1,859	2.64	1.06	27.8	4.5	6
Kouza-county		Samukawa	1.00	2.43	3,536	2.73	1.32	27.2	5.9	4
Naka-county		Oiso	2.10	2.24	1,901	2.73	1.07	28.5	4.6	7
		Ninomiya	1.00	1.28	3,301	2.70	1.04	28.6	4.2	3
Asigara-county		Nakai	0.00	1.54	506	3.10	1.06	27.6	4.1	0
Asigarakami-county		Oi	0.00	1.32	1,227	2.92	1.62	26.3	5.0	0
		Matsuda	0.00	1.17	324	2.71	0.93	26.6	4.3	0
		Yamakita	0.00	1.78	55	3.13	0.90	27.3	3.7	0
		Kaisei	1.40	1.28	2,361	2.94	1.64	27.1	8.0	2
Asigarashimo-county		Hakone	1.30	1.48	151	2.05	1.06	26.8	5.4	2
		Manazuru	0.00	2.80	1,234	2.61	1.19	26.4	3.9	0
		Yugawara	0.60	0.79	665	2.52	1.25	26.8	4.4	2
Aiko-county		Aikawa	0.90	3.48	1,225	2.76	1.17	25.8	5.3	3
		Kiyokawa-mura	3.00	4.48	50	3.03	0.98	28.3	3.4	1
	Average		1.02	2.08	5,581	2.52	1.19	27.84	6.03	14.18
	Standard deviation		0.55	0.79	4,103	0.27	0.14	0.72	1.40	11.25
	Median		1.00	1.96	5,489	2.55	1.20	28.02	5.93	13.50

*Standard population is 2005 data, **We calculated Kanagawa female's population for standard population (2005), Ascending order to JIS geographical name code(local government code)

Takahashi, 2005, 2012; Tango, 2008). We assumed the number of deaths or incidence to be Poisson distributed in each municipality. This method can detect clusters of any size and form located anywhere in the study region, whether or not they cross administrative borders.

The most likely cluster was defined as that with the maximum likelihood ratio. Statistical significance of clustering was based on Monte Carlo hypothesis testing (Tango, 2007), comparing the likelihood ratio test statistic from the observed data set with the test statistic from 999 random data sets generated under the null hypothesis of no clustering. The calculations were performed using the

Table 2. Breast Cancer Mortality and Incidence analysis in Kanagawa Prefecture, 2006 Using the Spatial Scan Statistic

Most Likely Cluster	Observed frequency	Expected frequency	SMR or SIR	LLR[a]	P[b]
Mortality :Tsurumi-ku, Kawasaki-ku, Saiwai-ku (3 regions)	74	54.17	1.37	3.52	0.53
Incidence: Nishi-ku, Naka-ku, Minami-ku, Hodogaya-ku, Isogo-ku, Kanazawa-ku, Kounan-ku, Sakae-ku, Yokosuka-city, Zushi-city, Hayama-twon (11regions)	1667	1236.42	1.35	89.9	0.001

[a], LLR = log likelihood ratio, [b],Significance of the identified clusters by the Monte Carlo test procedure.

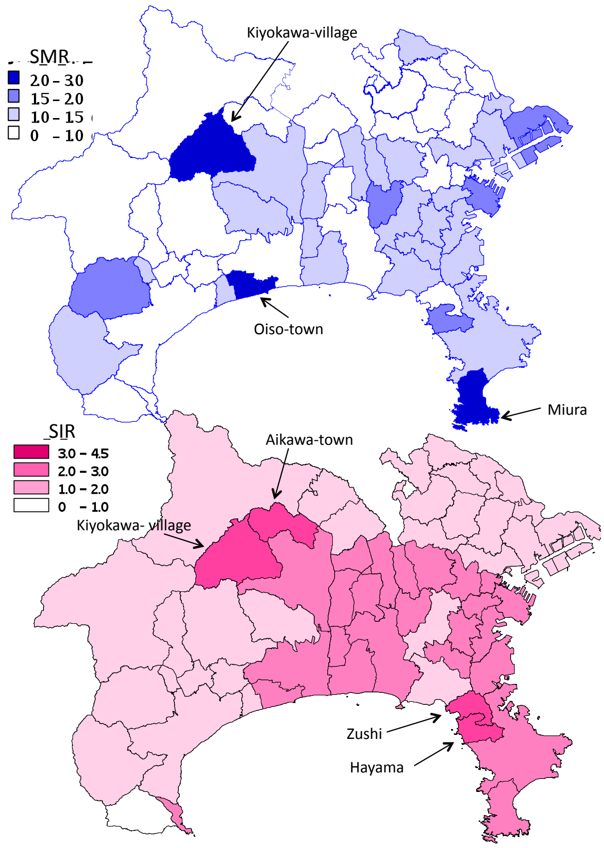

Figure 2. Breast cancer SMR and SIR in Kanagawa above SMR, below SIR

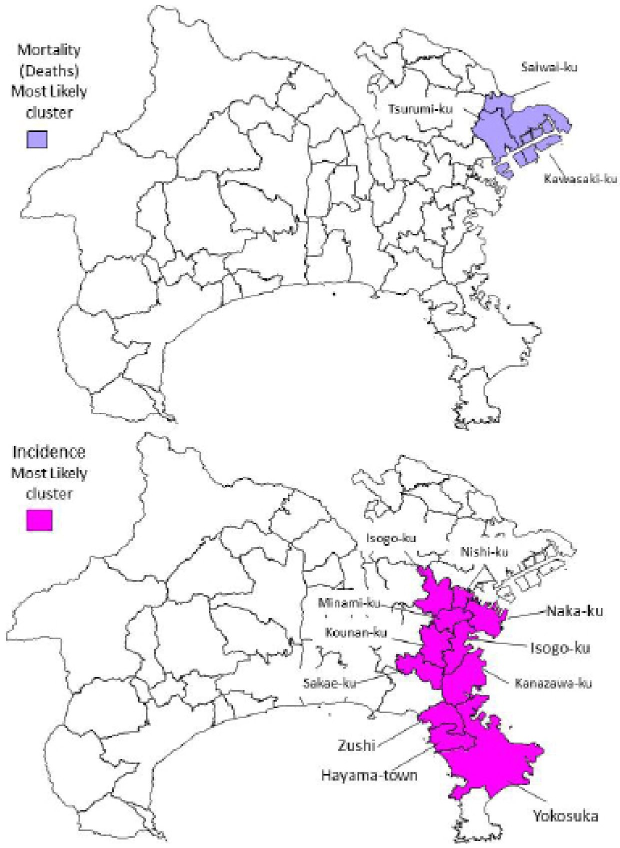

Figure 3. Geographic Clustering of Breast Cancer Mortality and Incidence in Kanagawa, Japan (2006). Dark color are most likely clusters, respectively [above; deaths was not statistically significant (p=0.53), below; incidence was statistically significant (p=0.001)]

program FlexScan version 3.1 developed by Takahashi et al (2010), designed specifically to implement spatial scan statistics.

To characterize a detected spatial cluster, we estimated the relative risk, observed number of cases divided by the expected number of cases within the clusters, which are also called SIR or SMR.

Student's t-test was performed to examine differences in socioeconomic variables, viz, persons per household, total fertility rate, age at first marriage for women, and marriage rate, between the most likely cluster and other regions were evaluated using SPSS version 19 (IBM SPSS Statistics).

Results

Table 1 shows population density, SMR, and SIR among women in Kanagawa Prefecture. Persons per household, total fertility rate, age at first marriage for women, and marriage rate were presented as reference indicators. Figure. 2 shows the distribution of SMR and SIR for breast cancer in Kanagawa. Three municipalities had particularly high SMR, viz Kiyokawa Village of Aiko County, Oiso Town of Naka County and Miura City. Four municipalities had particularly high SIR, viz Zushi City, Hayama Town, Kiyokawa Village of Aiko County, and Aikawa Town of Aiko County (Figure. 2). The flexible spatial scan statistic found the most likely cluster of breast cancer deaths in the area composed of three municipalities, Tsurumi-ku, Kawasaki-ku, and Saiwai-ku (Figure. 3), but it was not statistically siginificant (Table 2). The most likely cluster of incidence in the area composed of 11 municipalities, (Nishi-ku, Naka-ku, Minami-ku, Hodogaya-ku, Isogo-ku, Kanazawa-ku, Konan-ku, and Sakae-ku of Yokohama City, as well as Yokosuka City, Zushi City, and Hayama

Table 3. Differnce in Social-Economic Status between the Most Likely Cluster of Incidence and other Regions

	Most likely cluster	Other regions	P[a]
Persons per household	2.78±0.25(person)	2.55±0.27	0.055
Total fertility rate	1.13±0.09(person)	1.210±0.14	0.073
First-marriage age of women	28.2±0.43(years old)	27.8±0.75	0.017
Marriage rate	5.86±1.13(percent)	6.07±1.47	0.667

[a]; Student t-test

Town) are shown in Fig. 3. It was statistically siginificant (SIR=1.35, p=0.001). The method found the most likely cluster in a region encompassing the southeastern area in Kanagawa Prefecture, which a incidence rate 35 percent higher than tha rest of 45 municipalities. The most likely cluster was in the southeastern Kanagawa which were not high SIR four municipalities.

In the most likely cluster, age at first-marriage for women was 28.2±0.4 years old, which was significantly higher than other regions (p=0.017), whereas, total fertility rate, persons per household and marriage rate were not significantiy different (Table 3).

Discussion

Maps based on SMR and SIR by administrative division can visually show the geographical distribution of health affairs. Recently, the clustering method in spatial epidemiology has enabled statistical detection of the existence of clusters. The present study aimed to detect the presence or absence of clusters, viz, high mortality or incidence rate area through the use of breast cancer data for each city, town, and village in Kanagawa Prefecture.

Although the use of the maps based on SMR or SIR has been longstanding and widespread, SMR and SIR have also been discussed as problematic with respect to their functions as indicators (Tango, 2000). The biggest problems with these metrics are that SMR and SIR are affected by the population size of the subject region, and that SMR and SIR values are unstable in regions with particularly small populations, rendering them unsuited for regional comparison with other municipalities of different population sizes (Tango, 2000).

In this study, cluster detection test for breast cancer mortality in Kanagawa Prefecture demonstrated no clustering of mortality; regions with high SMR were not simply clusters of mortality from breast cancer. The disease maps which based on SIR and SMR revealed different distributions. Undeniably, observation is only the first step of the analysis, but an analysis method is needed to statistically determine whether disease clustering is present.

We used a spatial epidemiological clustering method to detect a cluster of breast cancer incidence in the southeast of Kanagawa Prefecture, and thus demonstrated the application of the method as a cluster detection test. Several prior studies have considered cluster detection test. One such study used data from 1978-1982 regarding 592 cases of leukemia and the population data for each of the 790 national census tracts in a region consisting of eight counties of New York in the United States (Alexander et al., 1992). This study is a widely known case of test method application proposed for the testing for spatial clustering (Openshaw et al., 1988; Waller et al., 1992). The northeastern United States is known for its high mortality due to breast cancer. Kulldorff et al (1997) conducted an analysis to determine whether regions with high breast cancer mortality are evenly distributed across the northeastern United States, or whether breast cancer is instead clustered in specific regions. To this end, they examined population data and mortality rate by age group from 1988-1992 for 244 counties of 11 states and the District of Colombia, a total of 245 counties. Their analyses identified most likely clusters, indicating that the high breast cancer mortality in some regions was not due to accidental error; this result held true even after adjustments were made to accommodate presumed confounding variables. SaTScan (circular scan method) of these previous studies is simple, the issue has been raised that only clusters of regions in circular shapes can be identified (Tango et al., 2007). On the other hand, with the flexible scan method also non-circular clusters can be identified, rendering complex shapes clearly identifiable that are otherwise not accessible.

In Japan, one out of every two persons is eventually diagnosed with some form of cancer (Matsuda et al., 2011). Because cancer is a disease of national importance, countermeasures are urgently needed. Particularly for breast cancer and other cancer types with relatively good prognoses and high survival rates, consideration of mortality data alone will not lead to effective countermeasures. In Kanagawa Prefecture, the five-year relative survival rate for breast cancer is high: 89.2 % (2005).

The geographical distributions of mortality and incidence point to different regions, which are apparent even upon visual inspection. In the incidence of breast cancer, it is critically important to identify the risk factors for cancer incidence and using the results of these analyses to inform prevention strategies. Several epidemiological studies have shown a connection between breast cancer risk and having received female hormone or experienced childbirth; the number of births also makes a contribution (Kelsey, 1993; Ewertz and Duffy, 1988; Fukuda et al, 2005). The identified most likely cluster region of this paper showed that women are getting married at later ages than other regions, and the connection with the precedence studies were suggested.

A limitation of our present study is that there are no data available at the smaller region level regarding the percentages of women who undergo breast cancer screening. Therefore, we referenced the data on breast cancer screening for all of Yokohama City as an indicator; very low screening rates were obtained: 9.5% in 2007, 11.3% in 2008, 14.5% in 2009, and 12.9% in 2010. The fact that clustering of incidence was observed in spite of the low screening rate implies that many cases are not detected in the early stages. Proactive measures are necessary to accelerate improvement of screening rates among the women living in regions showing clustering of breast cancer incidences.

In the population-based cancer registry of Kanagawa Prefecture for the year 2006, used in this study, the death certificate only (DCO) rate was 22.9%. DCO is a measure of the accuracy of cancer registration, and the lower the DCO rate, the better. The legal framework for population-based cancer-registry systems had not been established the past in Japan. In 2012, population-based cancer registries were initiated in all 47 prefectures of Japan, including the Tokyo metropolitan, and Cancer Registry Act was enacted in December 2013 finally.

Therefore, it is expected that accuracy will rapidly improve in the future. Enhanced accuracy of cancer-registry data across the country will increase the probability of successfully promoting effective cancer countermeasures that are grounded in science. Research regarding the effective use of cancer registry data should be conducted in such a way that it is widely acknowledged by the general public. It is one method to visualize the trend of cancer using maps.

In conclusion, we reported on smaller regions in Kanagawa Prefecture that exhibit clustering of breast cancer. This study methodology will be helpful in the analysis of geographical disparities in cancer mortality and incidence revealed in cancer registry data, for the purpose of eliminating regional disparities in cancer care. These maps should be regarded as tools for forming hypotheses leading to the next step of the study, for example, attempting to identify factors unique to the regions where clustering has been detected or identified. To establish cancer control and prevention measures in the future, it will be important to perform comparisons between smaller regions in each prefecture of Japan, and further research is needed to elucidate the contributing factors in clustering of breast cancer incidence.

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