

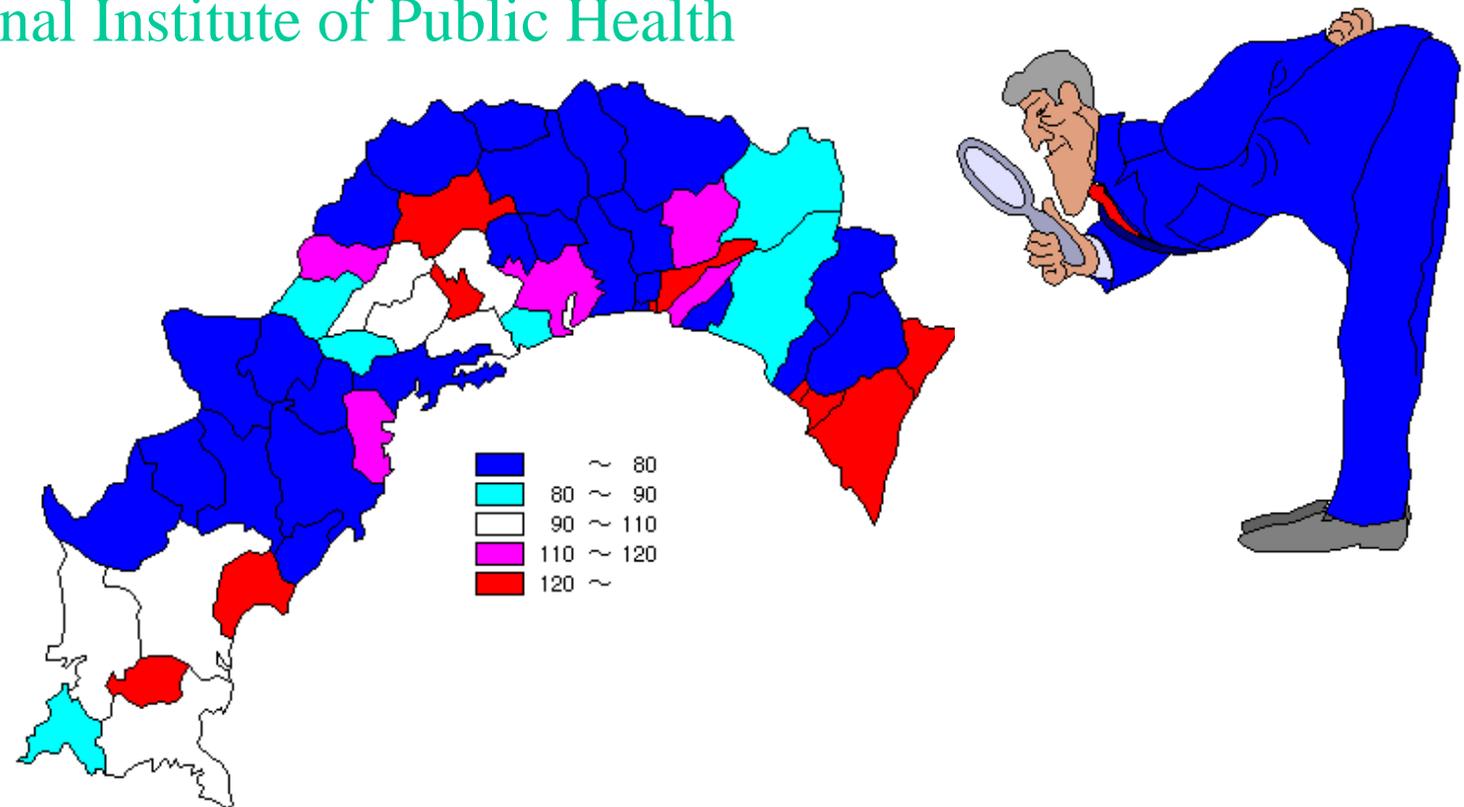
統計的発想を刺激する Visual tool: S-PLUS

研究事例: 疾病地図と疾病集積性について

Toshiro Tango

Departement of Technology Assessment and Biostatistics

The National Institute of Public Health

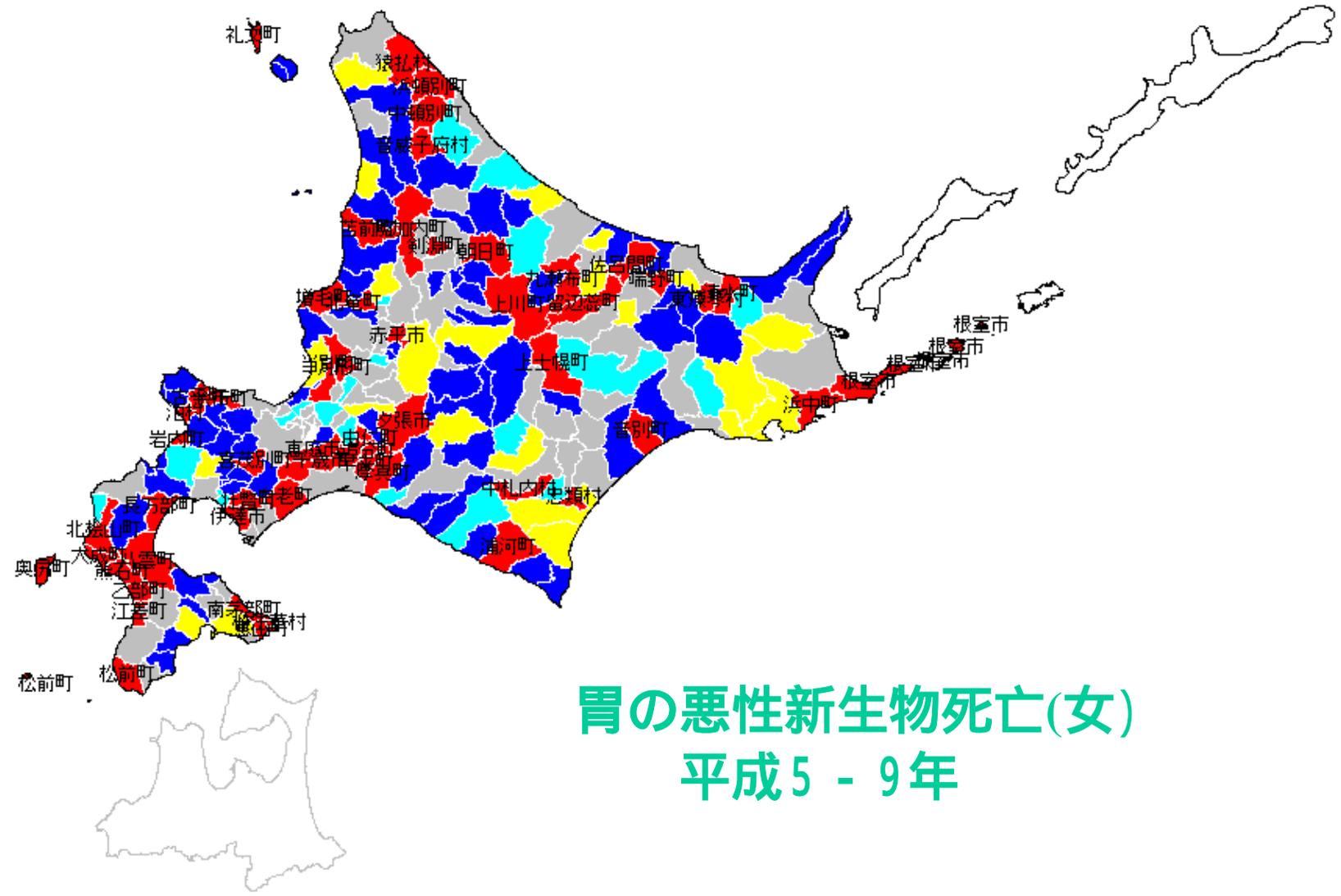
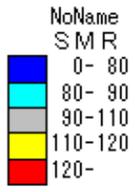


Copyright C.J.Imai

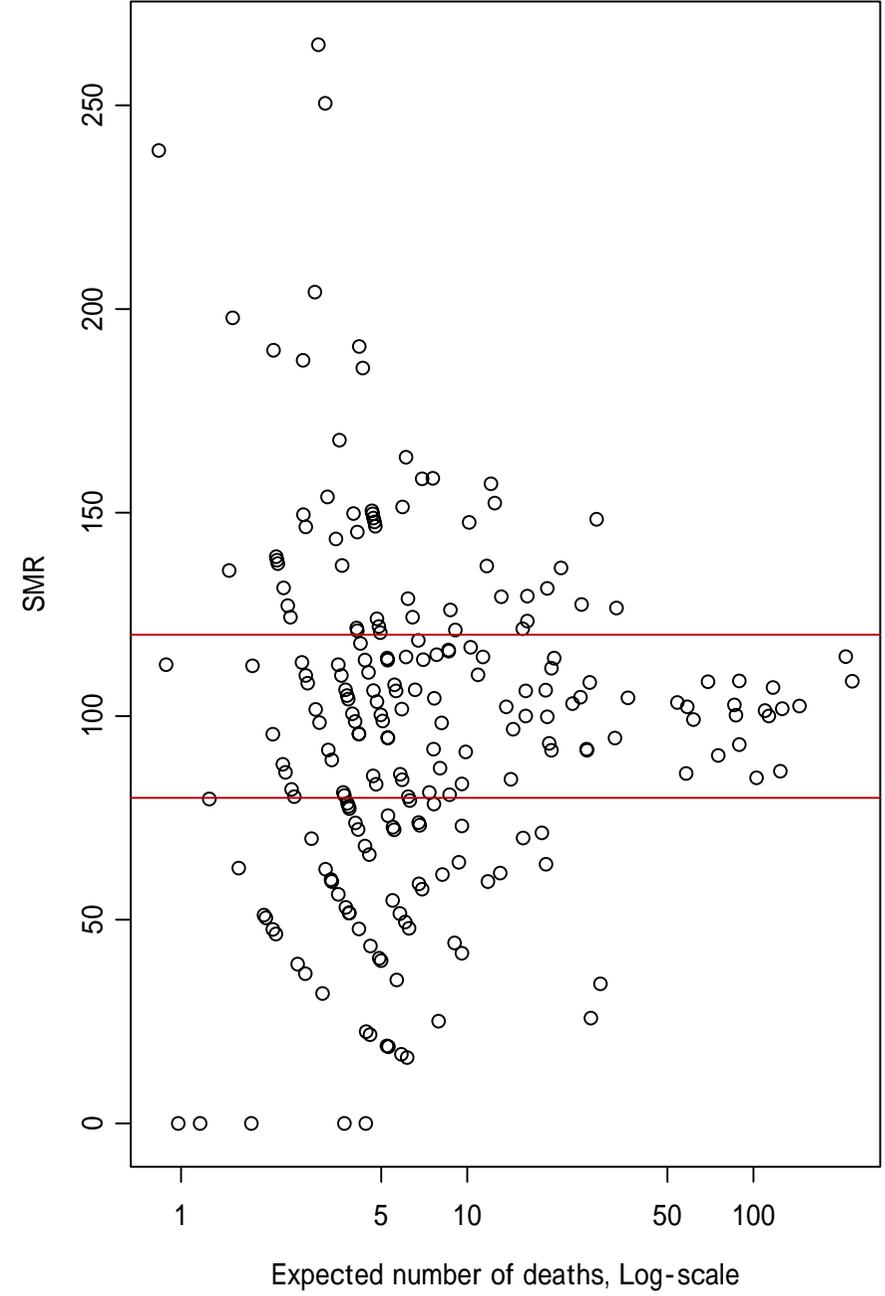
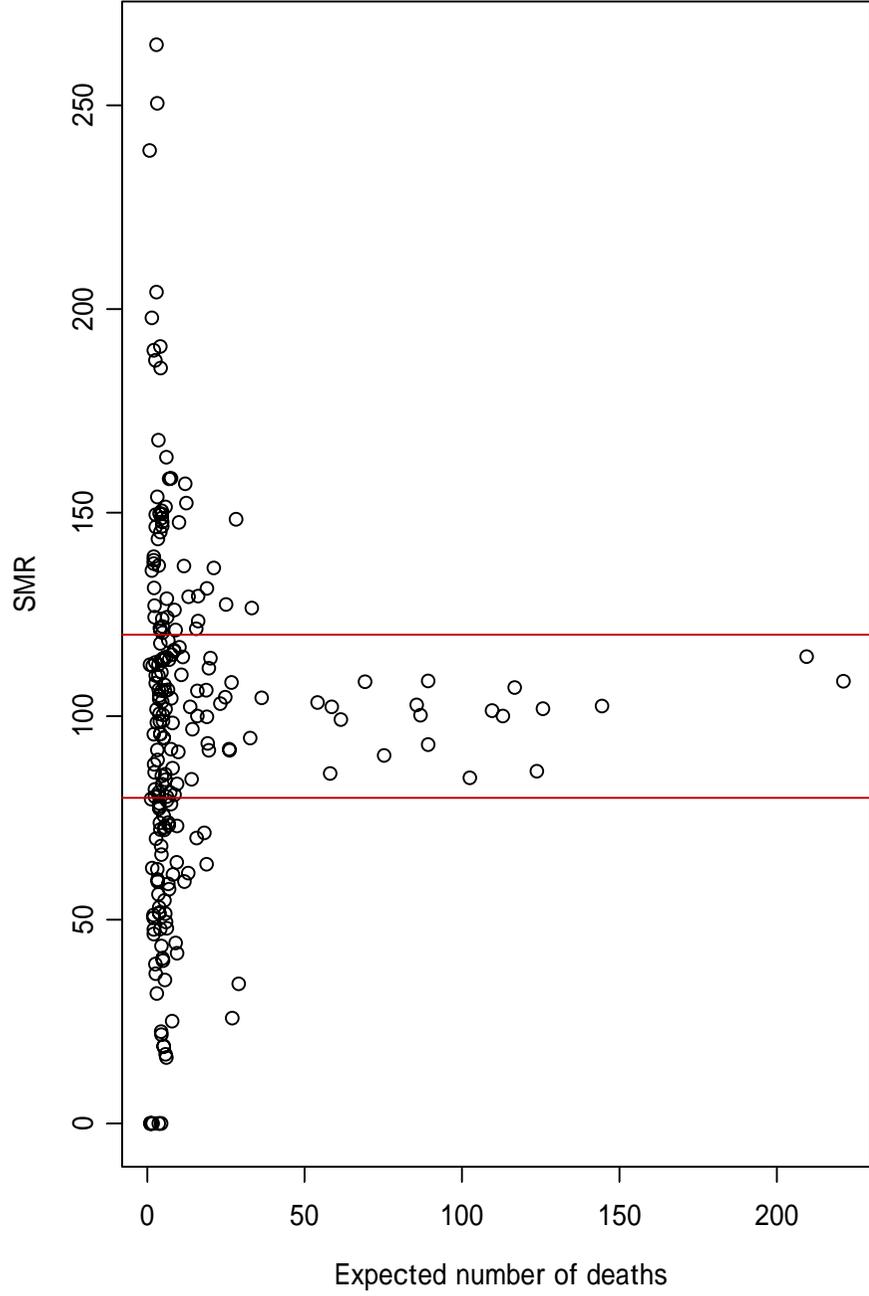
2004 S-PLUS Users' Conference

WHO専門者会議(1997, Rome) Disease Mapping and Risk Assessment for Public Health Decision Making

- 信頼性のある統計指標
- 国際比較が可能な統計指標
- 疾病地図の推定法
- 疾病の集積性を表現する指標



胃の悪性新生物死亡(女)
平成5 - 9年



健康指標の「計算」

$$\text{標準化死亡比} \stackrel{\text{def}}{=} \frac{\text{観測死亡数}}{\text{期待死亡数}}$$

$$\text{SMR} (\lambda) = \frac{d}{E} (\times 100)$$

健康指標の「推測」

$$\hat{\lambda} \stackrel{\text{Est.}}{=} \frac{\text{観測死亡数 } d}{\text{期待死亡数 } E}$$

< 仮定 >

λ : 未知のSMR

観測死亡数 d ----- ポアソン分布 (λE)

期待死亡数 $E = \sum_i (\text{人口})_i (\text{標準死亡率})_i$

λ を母数と考えた最尤推定値

統計的推測に関する二つの立場

Frequentist (頻度論学派)

λ を母数(定数)と考える

伝統的な統計学

Bayesian (ベイジアン, ベイズ学派)

λ を確率変数と考える

21世紀の統計学の方向

Frequentist

推定したいパラメータ λ は母数(定数)と考える

繰り返し可能な実験、標本調査を想定

頻度分布(ヒストグラム) => 確率分布

$f(\text{データ} | \text{パラメータ})$

(例) 死亡数 d ポアソン分布 $f(d | \lambda)$

計測値 x 正規分布 $f(x | \mu, \sigma^2)$

Bayesian

推定するパラメータ λ を定数と考えるのは不自然
(why?) ヒトの臨床検査値, 死亡率, などほとんどのパラメータは時間差, 地域差, 個人差などの不確実性 (variability) があるもの

λ も確率分布にしたがう確率変数と考える

繰り返し可能でない事象にも適用可能

(例:) あいつが彼を殺した確率は 0.9 以上だ!

Bayesian computation

- ・ パラメータ λ の不確実性を確率分布 $p(\lambda)$ (事前分布, prior distribution)
- ・ データの確率分布 $f(d | \lambda)$
- ・ **同時分布** $p(\lambda, d)$ を考えることができる
$$p(\lambda, d) = p(\lambda) f(d | \lambda)$$
- ・ **データをとる前の不確実性 $p(\lambda)$ をデータの情報で更新する. 更新された不確実性を $p(\lambda | d)$ (事後分布, posterior distribution)**
- ・ **点推定としては「事後分布の期待値(平均値)」**

事後分布の計算

--Bayesの定理--

$$\text{事後分布 } p(\lambda | \mathbf{x}) = \frac{p(\lambda, \mathbf{x})}{p(\mathbf{x})} = \frac{p(\lambda, \mathbf{x})}{\int p(\lambda, \mathbf{x}) d\lambda}$$

$$= \frac{p(\lambda) f(\mathbf{x} | \lambda)}{\int p(\lambda) f(\mathbf{x} | \lambda) d\lambda}$$

$$\propto p(\lambda) f(\mathbf{x} | \lambda) = \text{事前分布} \times \text{尤度}$$

Bayesianの問題

- ・ 事前分布 $p(\lambda)$ の選び方
 - 従来: 自然共役(natural conjugate)
 - 最近: なんでもO.K.
- ・ 事前分布 $p(\lambda)$ に含まれるパラメータの推定法
 - Full Bayes: パラメータも確率変数
 - Empirical Bayes: データから推定
- ・ Bayesの定理に含まれる積分の計算法
 - 従来: 不可能であきらめることが多かった
 - 最近: Markov Chain Monte Carlo

Empirical Bayes estimate for SMR

観測死亡数 d_k は期待死亡数 $\lambda_k E_k$ をもつポアソン分布：

$$f(d_k | \lambda_k, E_k) = \frac{(\lambda_k E_k)^{d_k} \exp(-\lambda_k E_k)}{d_k!}$$

パラメータ λ_k の事前分布にはガンマ分布：

$$g(\lambda_k | \alpha, \beta) = \frac{\alpha(\alpha\lambda_k)^{\beta-1} \exp(-\alpha\lambda_k)}{\Gamma(\beta)}$$

$$E(\lambda_k) = \frac{\beta}{\alpha}$$

$$\text{Var}(\lambda_k) = \frac{\beta}{\alpha^2}$$

ポアソン分布とガンマ分布は自然共役

λ_k の事後分布は Bayes の定理より, $\boldsymbol{\eta} = (\alpha, \beta)$ とおいて、

$$h(\lambda_k | E_k, d_k, \boldsymbol{\eta}) = \frac{p(\lambda_k | \boldsymbol{\eta}) f(d_k | \lambda_k, E_k)}{\int_0^\infty p(\lambda_k | \boldsymbol{\eta}) f(d_k | \lambda_k, E_k) d\lambda_k}$$

したがって、SMR(= λ_k) の推測は、事後分布からの期待値

$$\begin{aligned} \hat{\lambda}_k &\Leftarrow E(\lambda_k | E_k, d_k, \boldsymbol{\eta}) = \int_0^\infty \lambda_k h(\lambda_k | E_k, d_k, \boldsymbol{\eta}) d\lambda_k \\ &= \frac{\int_0^\infty \lambda_k p(\lambda_k | \boldsymbol{\eta}) f(d_k | \lambda_k, E_k) d\lambda_k}{\int_0^\infty p(\lambda_k | \boldsymbol{\eta}) f(d_k | \lambda_k, E_k) d\lambda_k} \end{aligned}$$

事後分布 h もガンマ分布

Bayes 推定値は

$$\begin{aligned}\hat{\lambda}_{EB,k} &= \frac{\hat{\beta} + d_k}{\hat{\alpha} + E_k} \\ &= \frac{E_k}{\hat{\alpha} + E_k} \frac{d_k}{E_k} + \frac{\hat{\alpha}}{\hat{\alpha} + E_k} \frac{\hat{\beta}}{\hat{\alpha}}\end{aligned}$$

となる。この式の形から $\hat{\lambda}_{EB,k}$ は

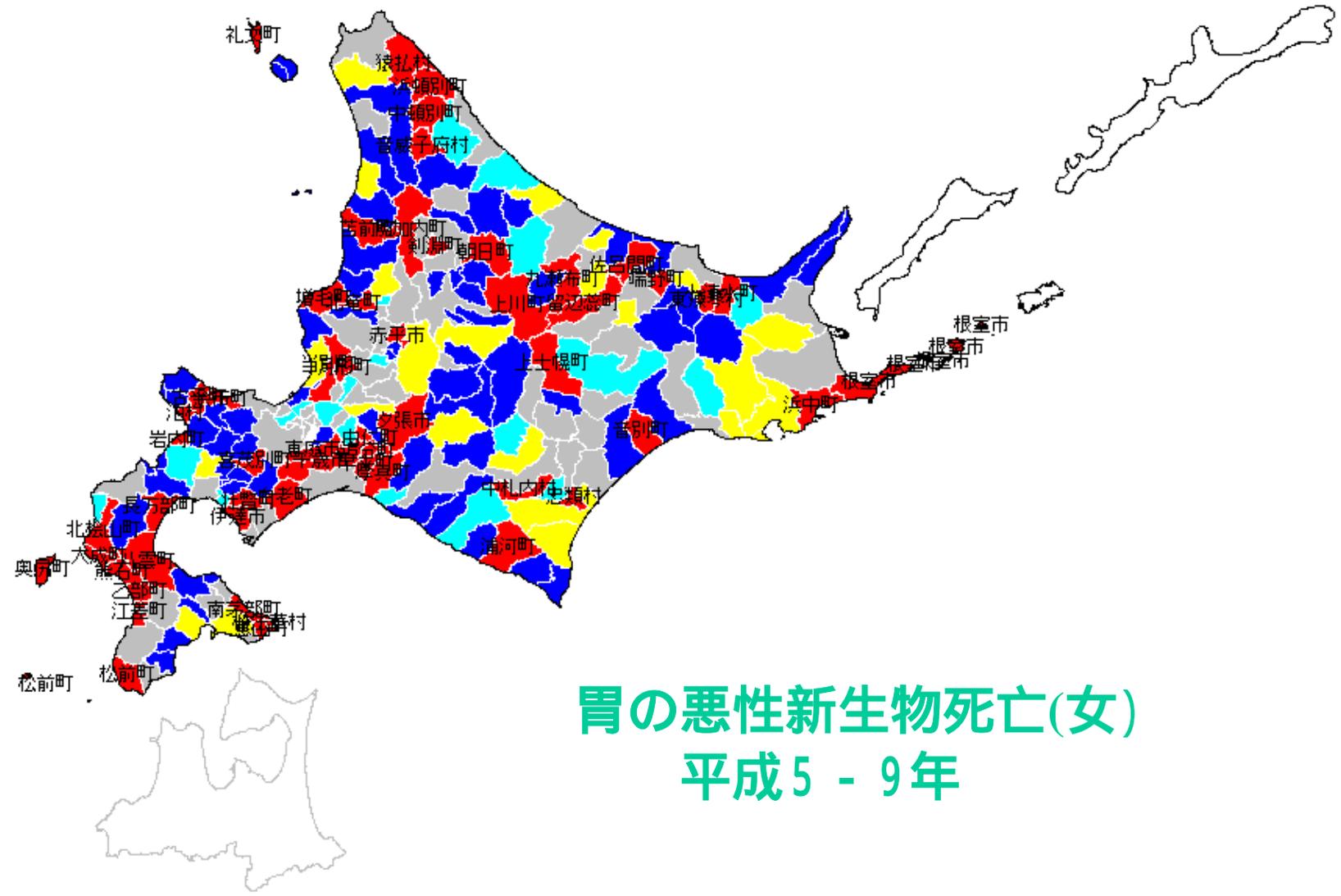
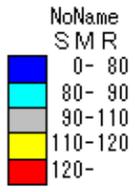
- 1) 人口が大きい場合には ($E_k \rightarrow$ 大)、通常の標準化死亡比 $\hat{\lambda}_k = d_k/E_k$ に近づき、
- 2) 人口が少ない場合には ($E_k \rightarrow$ 小)、地域全体の平均値 $\hat{\beta}/\hat{\alpha}$ に近づく。

Bayesian inference

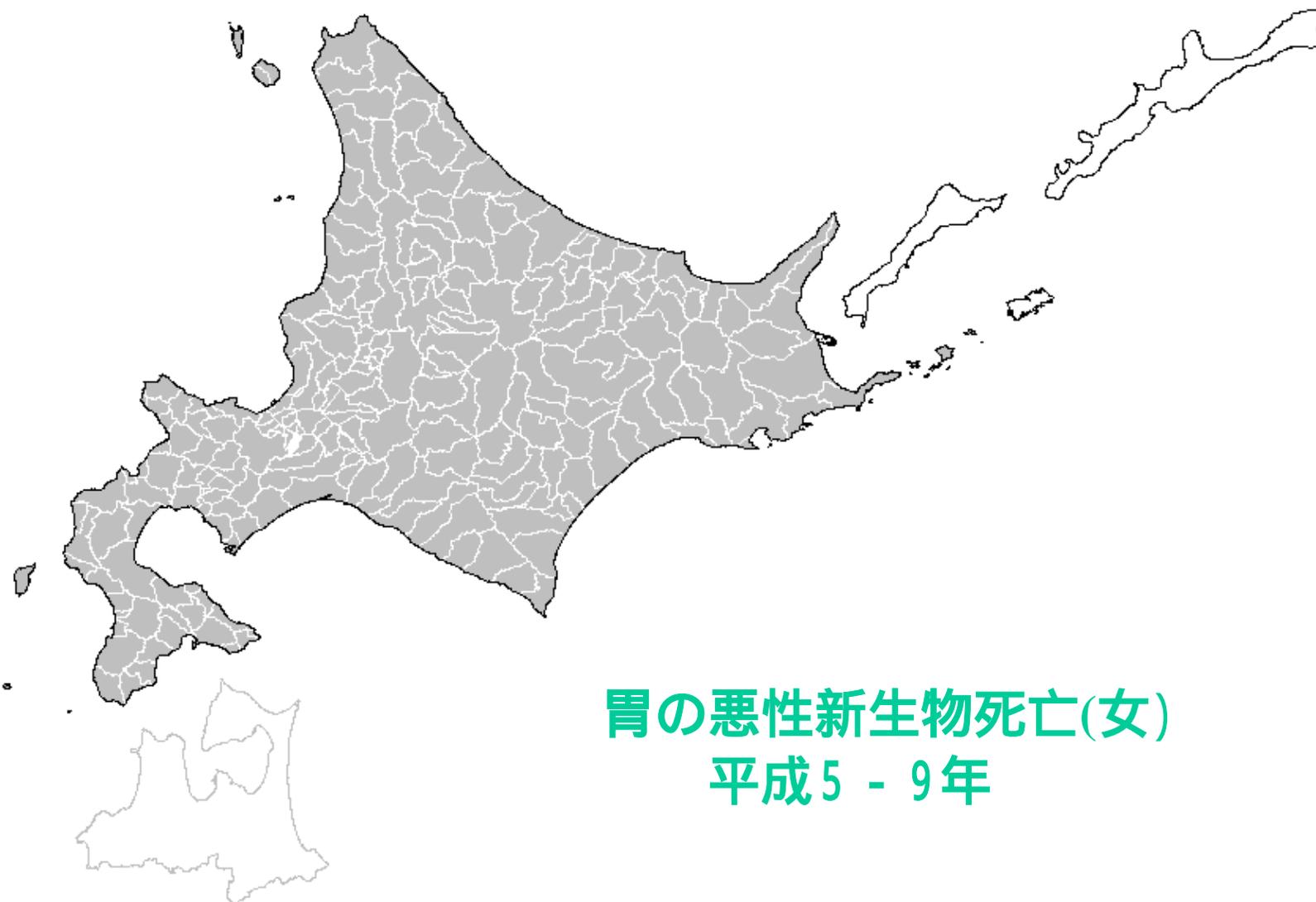
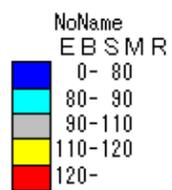
- ・ 情報の無いときは地域全体の平均値
- ・ 情報が増加してくればその地域のデータ



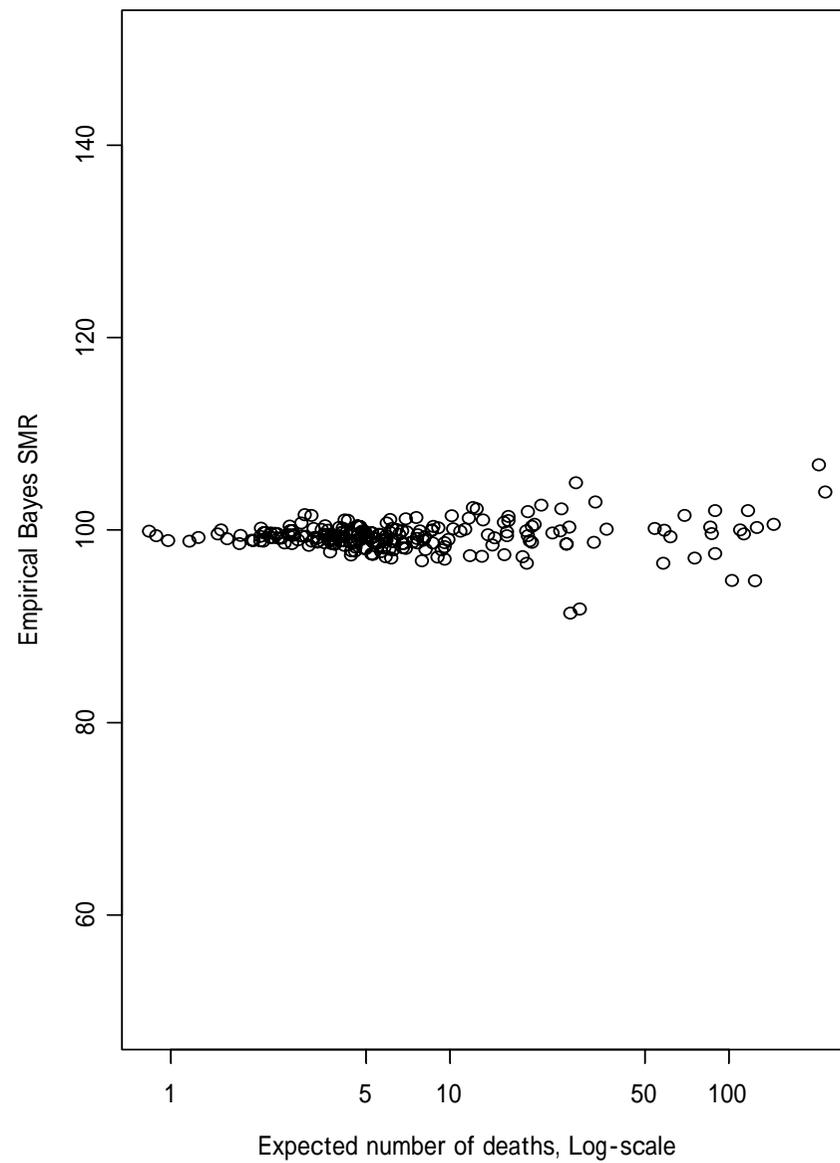
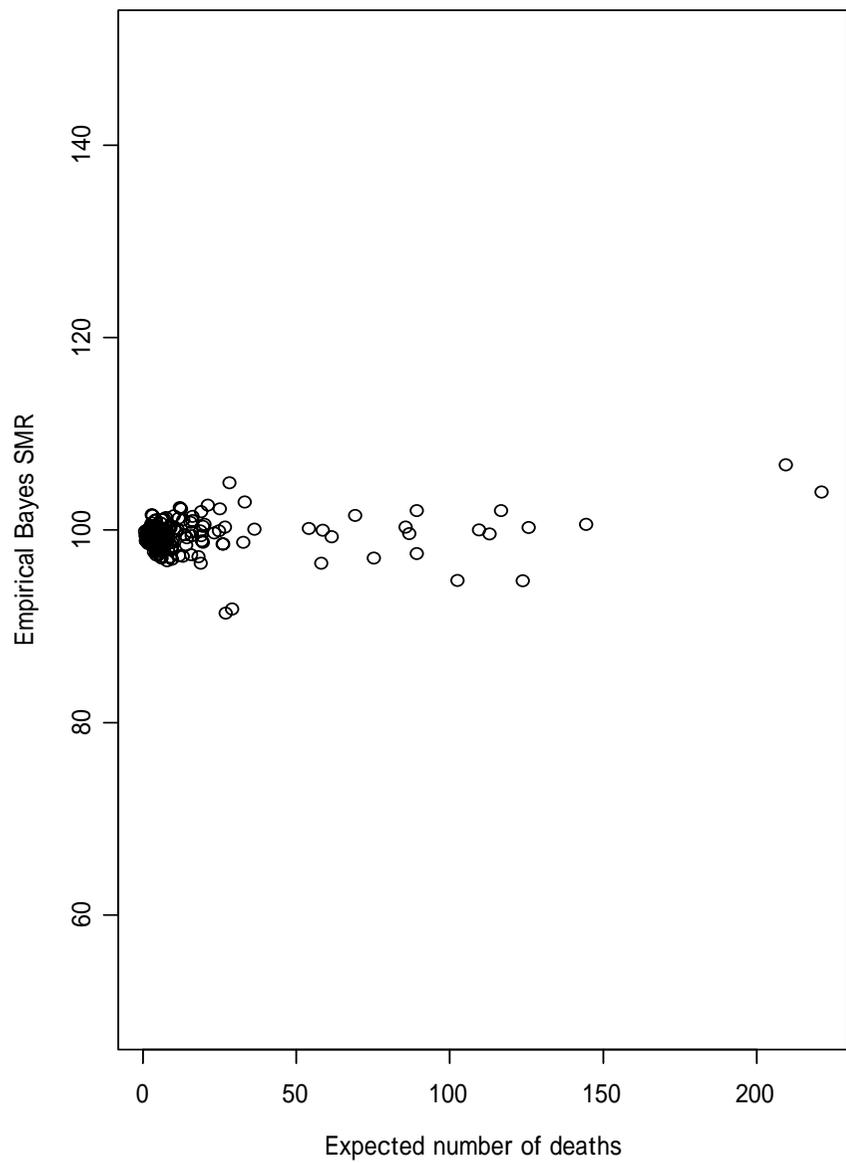
- ・ 診断・治療における臨床検査値の読み方
 - 1) 初診時に正常範囲(他のヒトのデータ)
 - 2) 入院患者の状態は患者の過去のデータ



胃の悪性新生物死亡(女)
平成5 - 9年



胃の悪性新生物死亡(女)
平成5 - 9年



c:\tan\asak\aaa.dvi - dviout

File Jump Search Display View Option Help

1 (1)

An ordinary ecological regression

このような図を見ると、論文等でよくみかける次のような回帰分析が如何に馬鹿げているか理解できるはずである。

$$\text{SMR} = \beta_0 + \beta_1 x_1 + \cdots + \beta_m x_m + \text{誤差}$$

このように、地域の比較を行うためには、「人口の大きさを調整」しなければならない。

Page: 1/7, number 1/7 dpi: x=300/2, y=300/2 Gamma = 800/1000 Size: x = 21.00cm, y = 29.70cm

スタート Microso... MS-DO... S-PLUS... イクスプ... aaa.tex ... Jniph99... c:\tan... 22:21

疾病の集積性

- ・ Bayesian approach は人口のサイズを調整する方法として重要であることを解説した
- ・ しかし、どんな指標であっても小さい順に並べれば必ず、最小値、最大値が存在する
- ・ 本当に健康の良い、思わしくない地域の同定は



- ・ **疾病の集積性の検定**
(Test for disease clustering)

疾病の集積性検定のタイプ

Global test:

- ・ Study area の特定の地域(未知)に疾病が集積している？
- ・ 感染症のように地域のいたるところで集積性が点在している？

Focused test:

- ・ 原発施設、ごみ焼却施設、危険物廃棄施設等の周辺に疾病が集積している？

二つの集積性検定

Kulldorff 's Spatial Scan Test:

- ・ 集積している地域の推定
- ・ 過疎地域の集積性の検出力が高い
(1995, Stat in Med; 1997, Com in Stat)

Tango's Maximized Excess Events Test:

- ・ Tango's index (1984, Biometrics) の拡張
- ・ 集積している地域の中心を推定
- ・ 都市部の集積性の検出力が高い
(1995, 2000, Stat in Med)

Focused test :

Tango(1995, 2000)

$$d_k \sim \text{Poisson}(E(d_k)), \quad k = 1, \dots, K$$

$$H_0 : E(d_k) = \tau n_k, \quad \text{no clustering}$$

$$H_1 : E(d_k) = \tau n_k (1 + a_{k,k_0} \theta), \quad \text{cluster around } k_0$$

$$a_{kh}(\lambda) = \exp\left\{-4\left(\frac{d_{kh}}{\lambda}\right)^2\right\}$$

$$d_{kh} = \text{distance between } (k, h)$$

where λ denotes the cluster size.

Efficient score for this test is

$$\begin{aligned}
 U_{k_0}(\lambda) &= \sum_{k=1}^K a_{k_0,k}(\lambda)(d_k - E(d_k)) \\
 &= \sum_{k=1}^K w_{k_0} a_{k_0,k}(\lambda)(d_k - E(d_k))
 \end{aligned}$$

where $w_k = 1(k = k_0); = 0$ (otherwise). When the cluster region is unknown, by putting $w_k = d_k - E(d_k)$, the above score can lead to a **Global test**:

$$C_\lambda = \sum_{k=1}^K \left\{ \sum_{h=1}^K a_{k,h}(\lambda) (d_k - E(d_k))(d_h - E(d_h)) \right\}$$

$$= \sum_{k=1}^K U_k(\lambda) \sim \chi^2 \text{ approximation (quite good)}$$

$$P_{min} = \min_{\lambda} \Pr \{ C_\lambda > c_\lambda \mid H_0, \lambda \}$$

$$= \Pr \{ C_\lambda > c_\lambda \mid H_0, \lambda = \lambda^* \}$$

where λ should move in the range $0 < \lambda \leq d_{max}/4$.

If test result is significant, the most likely cluster center could be the region which has the largest contribution in terms of

$$\frac{U_k(\lambda^*)}{C_{\lambda^*}} \times 100(\%)$$

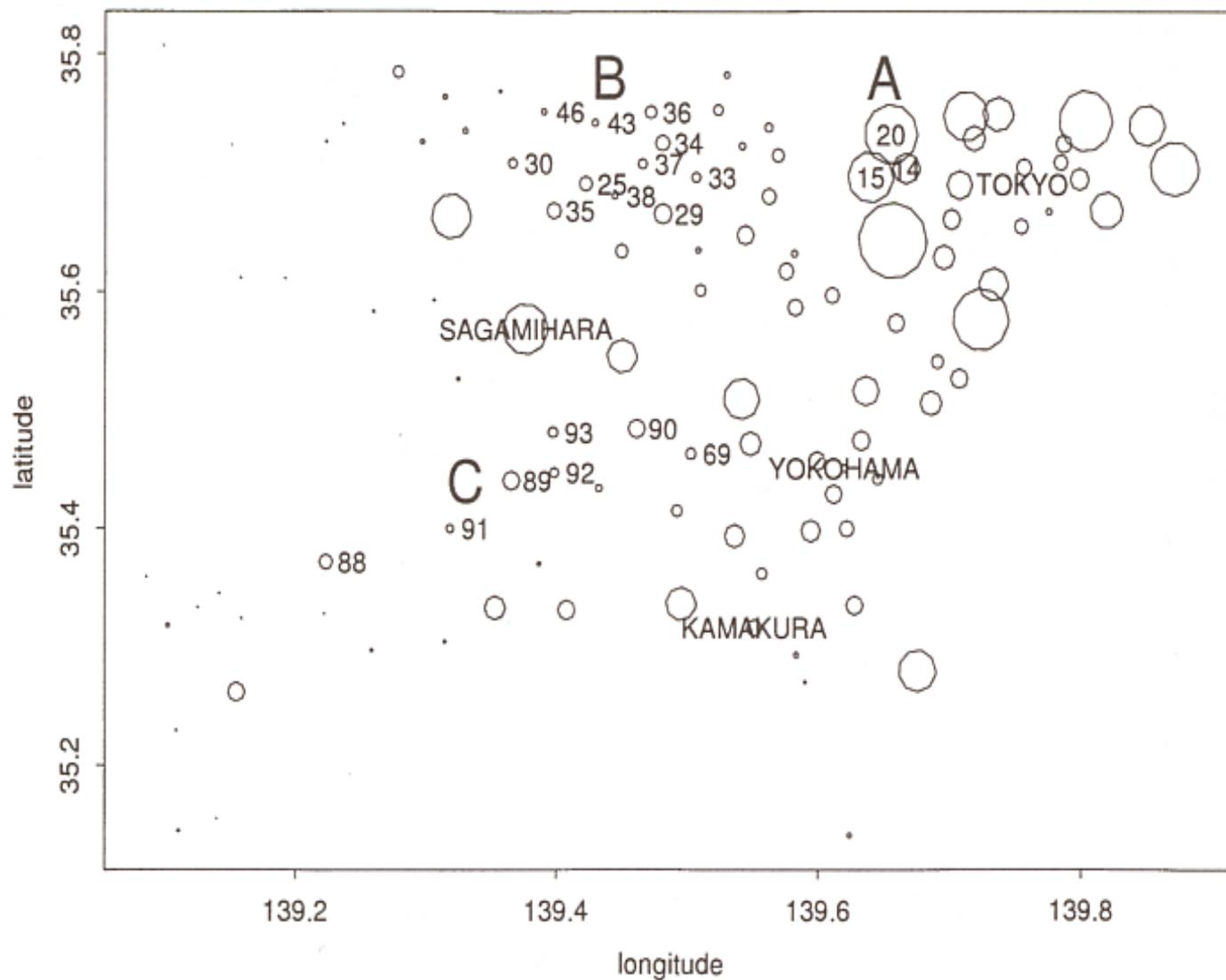


Figure 1. The 113 regions comprising wards, cities and villages in the area of Tokyo Metropolis and Kanagawa prefecture in Japan. The centre of a circle is the location of population centroid of the corresponding region and the radius is set proportional to the population size. Three types of clusters are indicated by region numbers and symbols 'A', 'B' and 'C'. For more details, see text

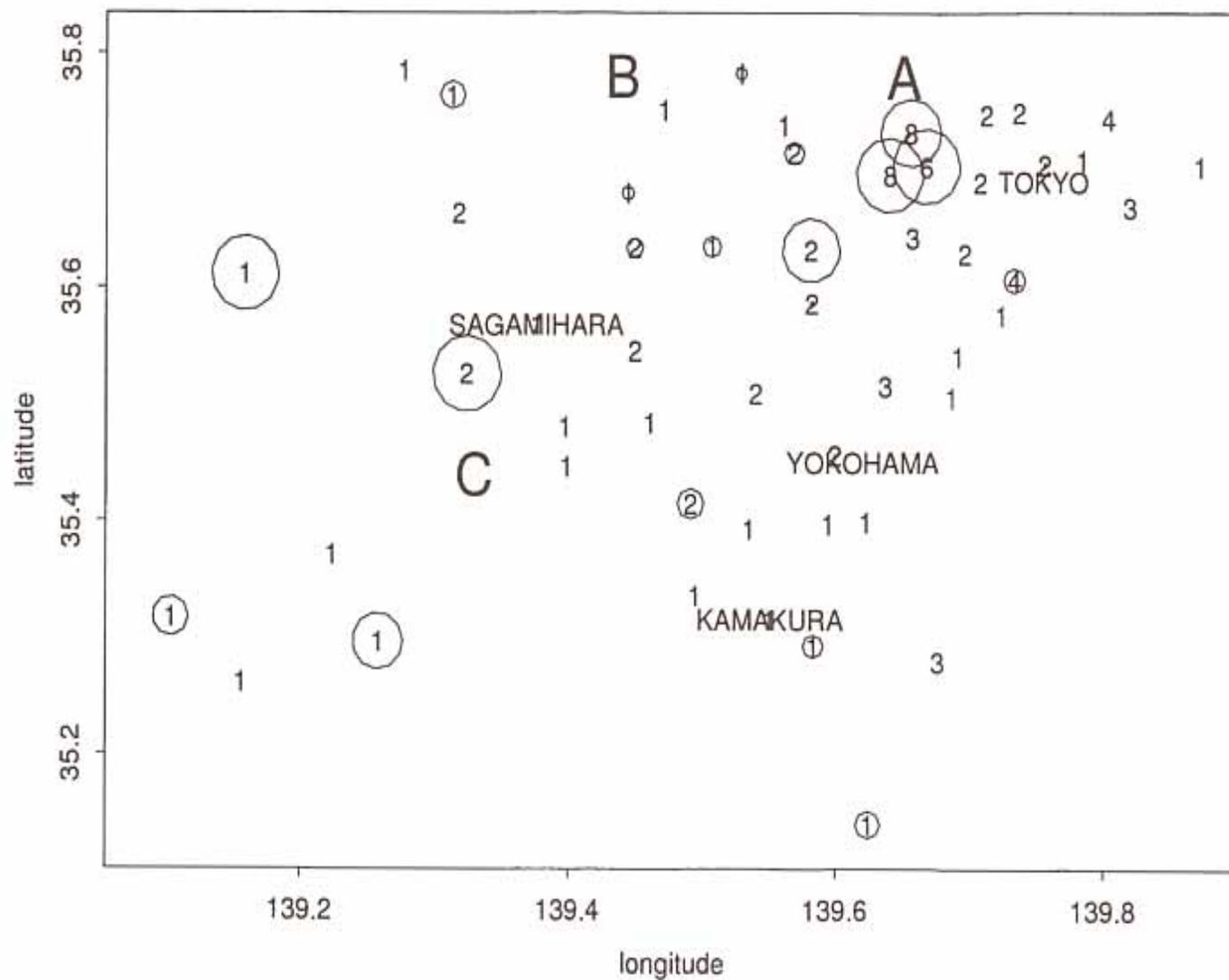
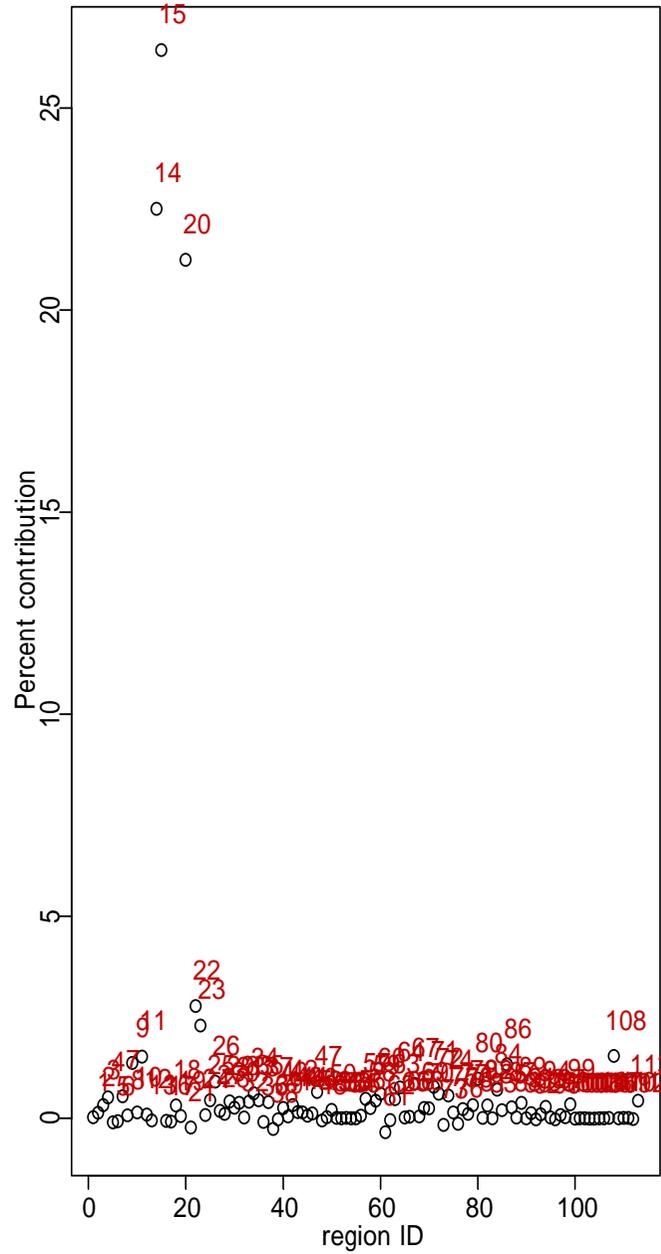
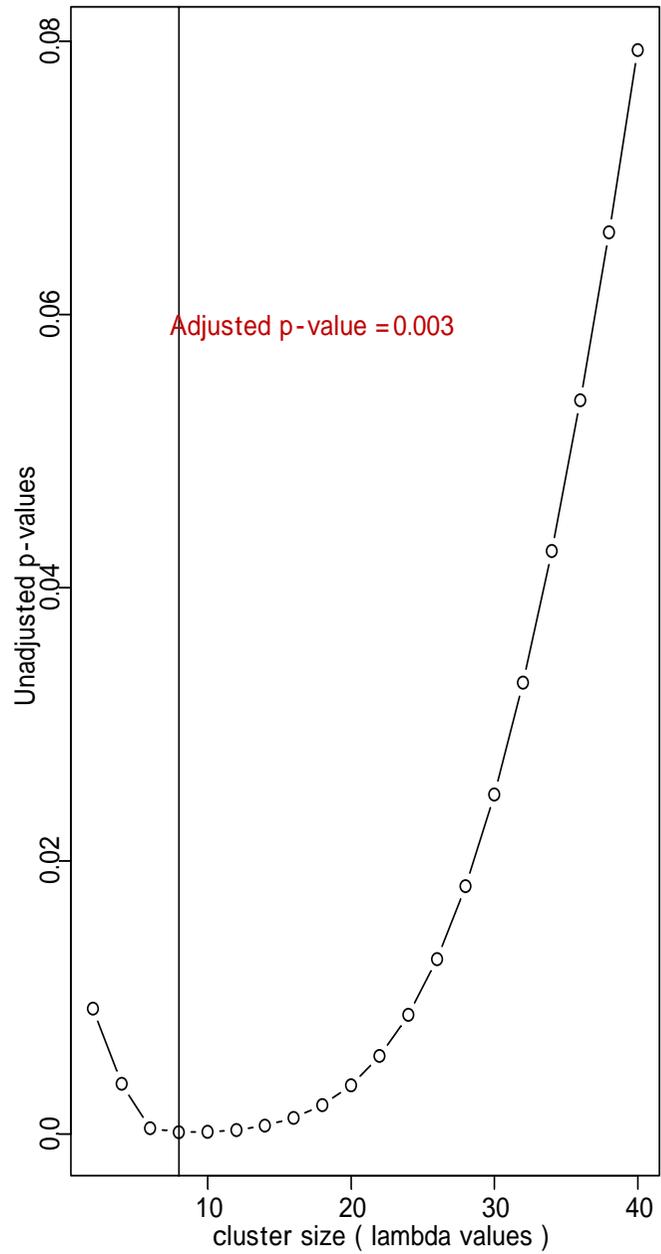


Figure 2. A random sample from clustering model A. Circles are drawn only for the regions whose standardized risk ratios are statistically significantly larger than 1 at $\alpha = 0.05$. The radius is set inversely proportional to the tail probability. The number shown in the map indicates the number of observed cases $n_i(> 0)$



Department of Technology Assessment and Biostatistics

ダウンロード

S-PLUS code for the detection of spatial clustering program called MEET (Maximized Excess Events Test)

OS / Language:	S-PLUS
Reference:	Tango T. A TEST FOR SPATIAL DISEASE CLUSTERING ADJUSTED FOR MULTIPLE TESTING. <i>Statistics in Medicine</i> . 2000;19:191-204.
How to use:	See the program and sample outputs .
Download: (click the file name to start downloading):	Download 'meet.s' to your computer and run it in S-PLUS. Program: meet.s Manual: See the reference article.

[ダウンロードトップページへ戻る](#)

Spatial scan statistic (Poisson model)

--- Kulldorff (1997)

Assume that the study area consisting of m regions and the number of cases X_i in the region i is a Poisson random variable,

$$X_i \stackrel{\text{i.i.d.}}{\sim} \text{Po}(\eta_i p_i) \quad (i = 1, 2, \dots, m)$$
$$\eta_i > 0, \quad 0 < p_i < 1$$

Define the **windows** Z (the set of regions) and the **collection** Ω of all the windows. Then, for some $Z (\in \Omega)$, we consider the **hot spot model**:

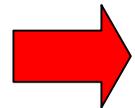
$$p_i = p \quad (i \in Z); \quad p_i = q \quad (i \notin Z)$$

Spatial scan statistic (Poisson model)

$$H_0 : p = q \quad H_1 : p > q$$

$$n(Z) := \sum_{i \in Z} x_i, \quad \mu(Z) := \sum_{i \in Z} \eta_i, \quad G = Z \cup Z^c$$

$$\lambda := \sup_{Z \in \Omega} \frac{\left(\frac{n(Z)}{\mu(Z)}\right)^{n(Z)} \left(\frac{n(Z^c)}{\mu(Z^c)}\right)^{n(Z^c)}}{\left(\frac{n(G)}{\mu(G)}\right)^{n(G)}} I \left(\frac{n(Z)}{\mu(Z)} > \frac{n(Z^c)}{\mu(Z^c)} \right)$$

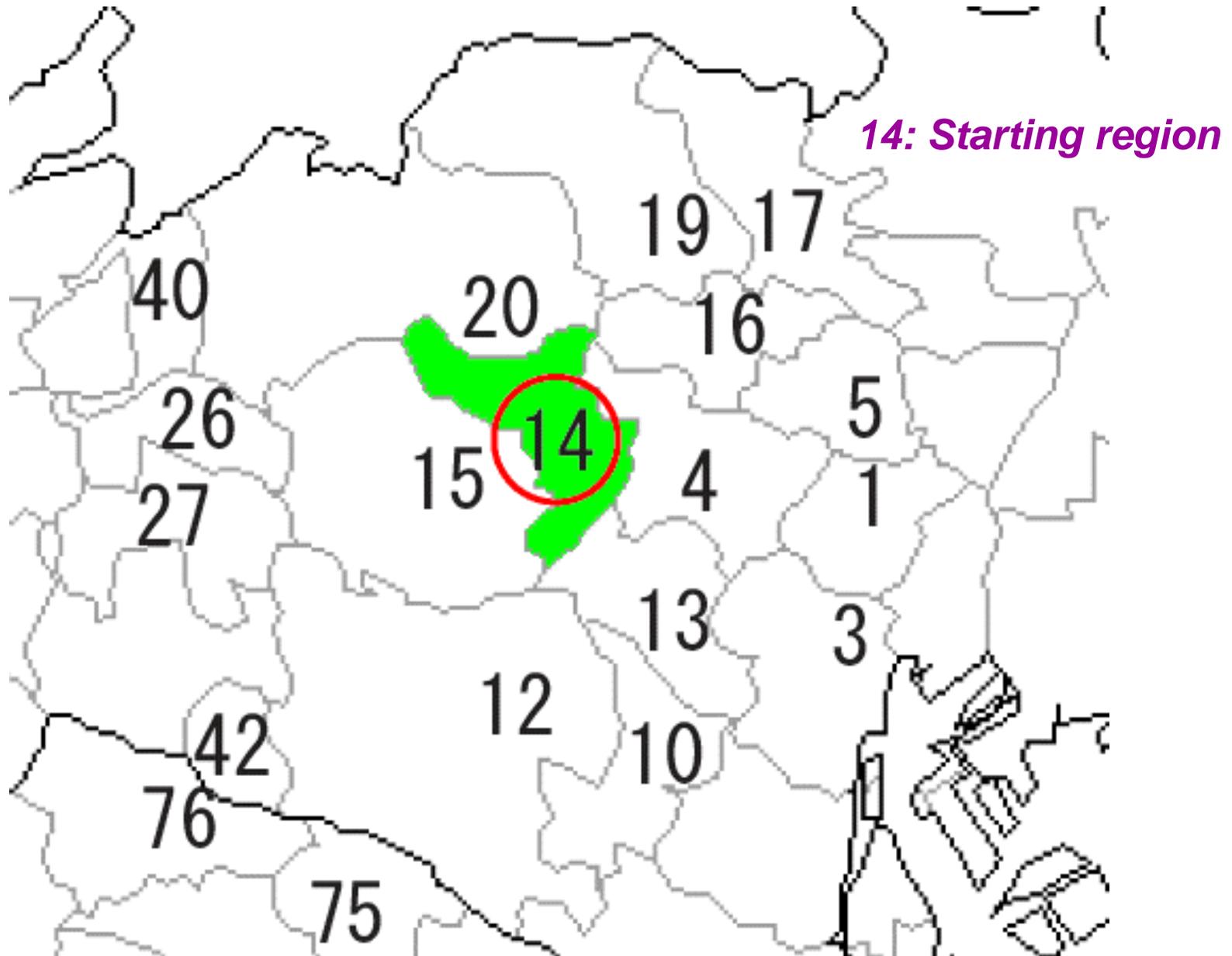


The window $Z (\in \Omega)$ which attains the maximum likelihood is defined as the most likely cluster (MLC).

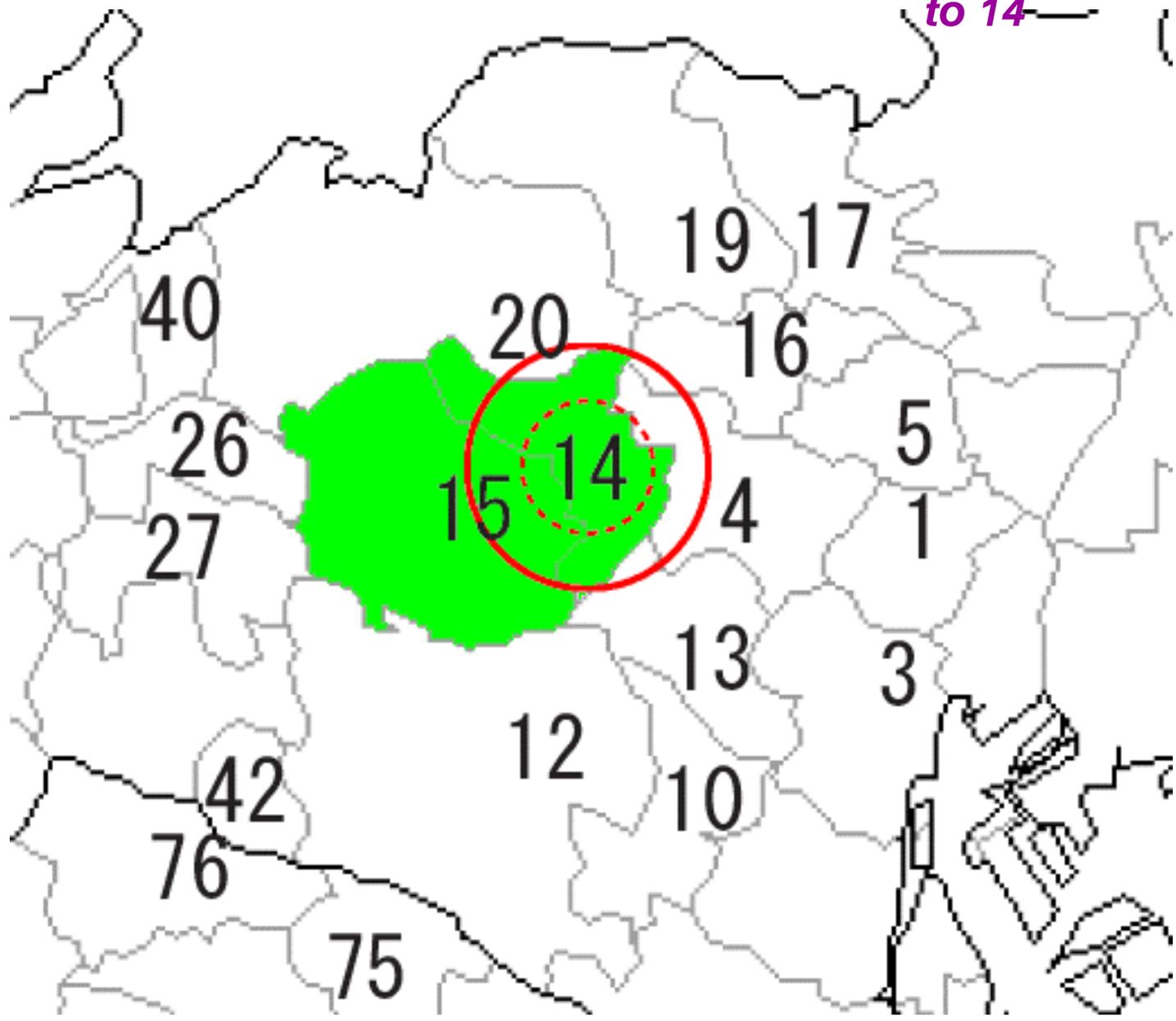
Note: The null distribution of λ is calculated by Monte Carlo samplings

Kulldorff's spatial scan

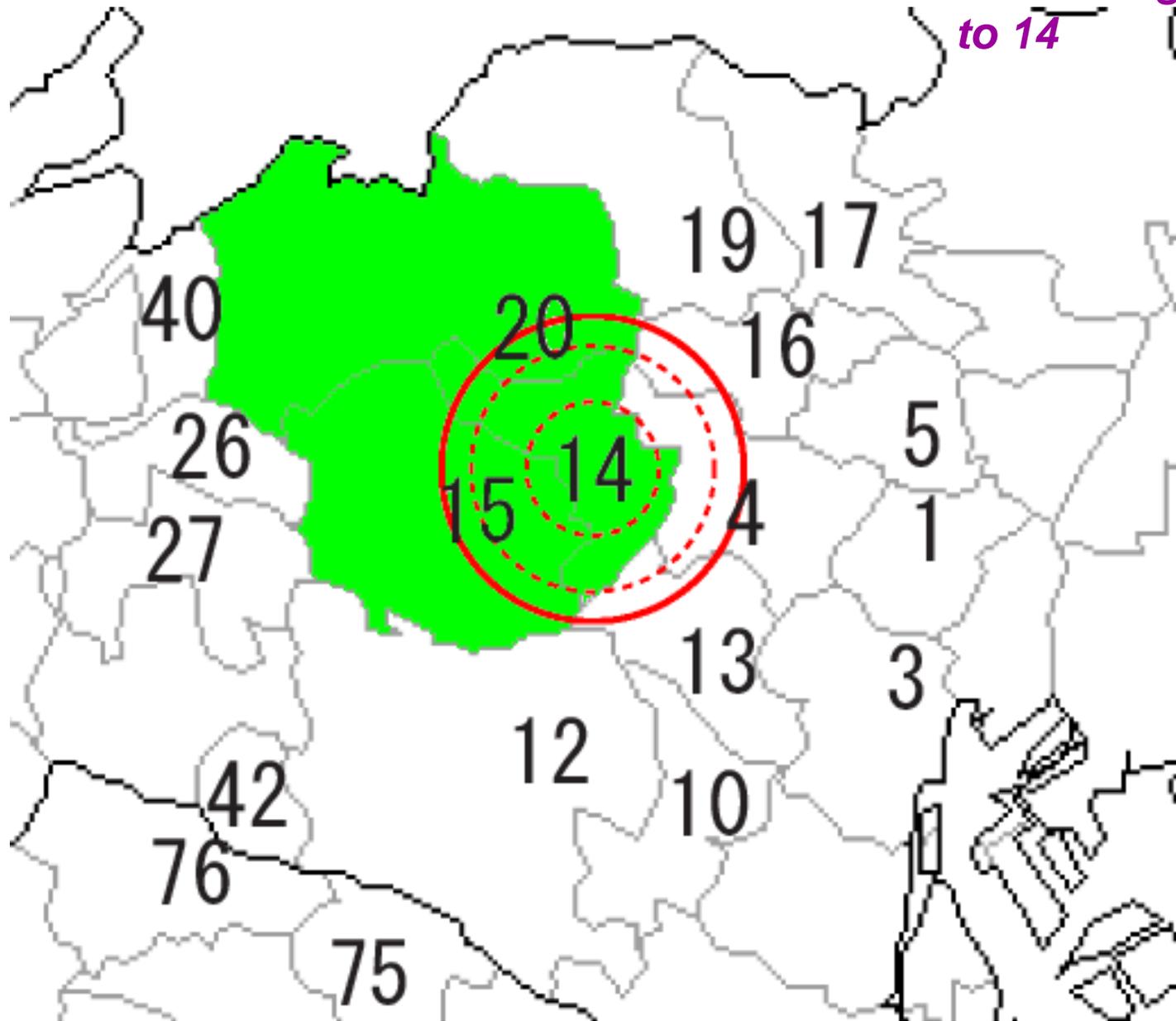
Let $K = 15$.



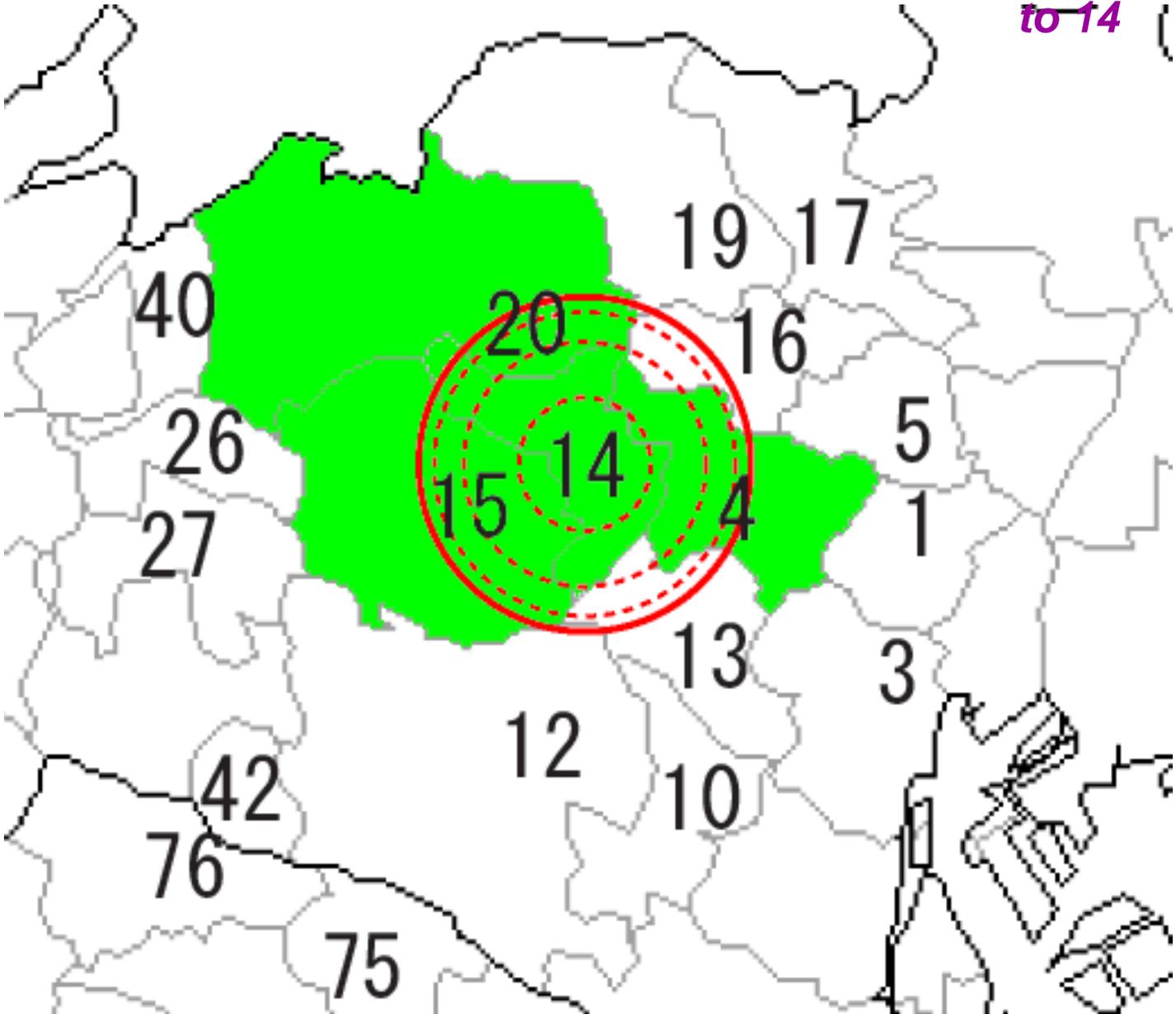
15: 1st-Nearest neighbour to 14



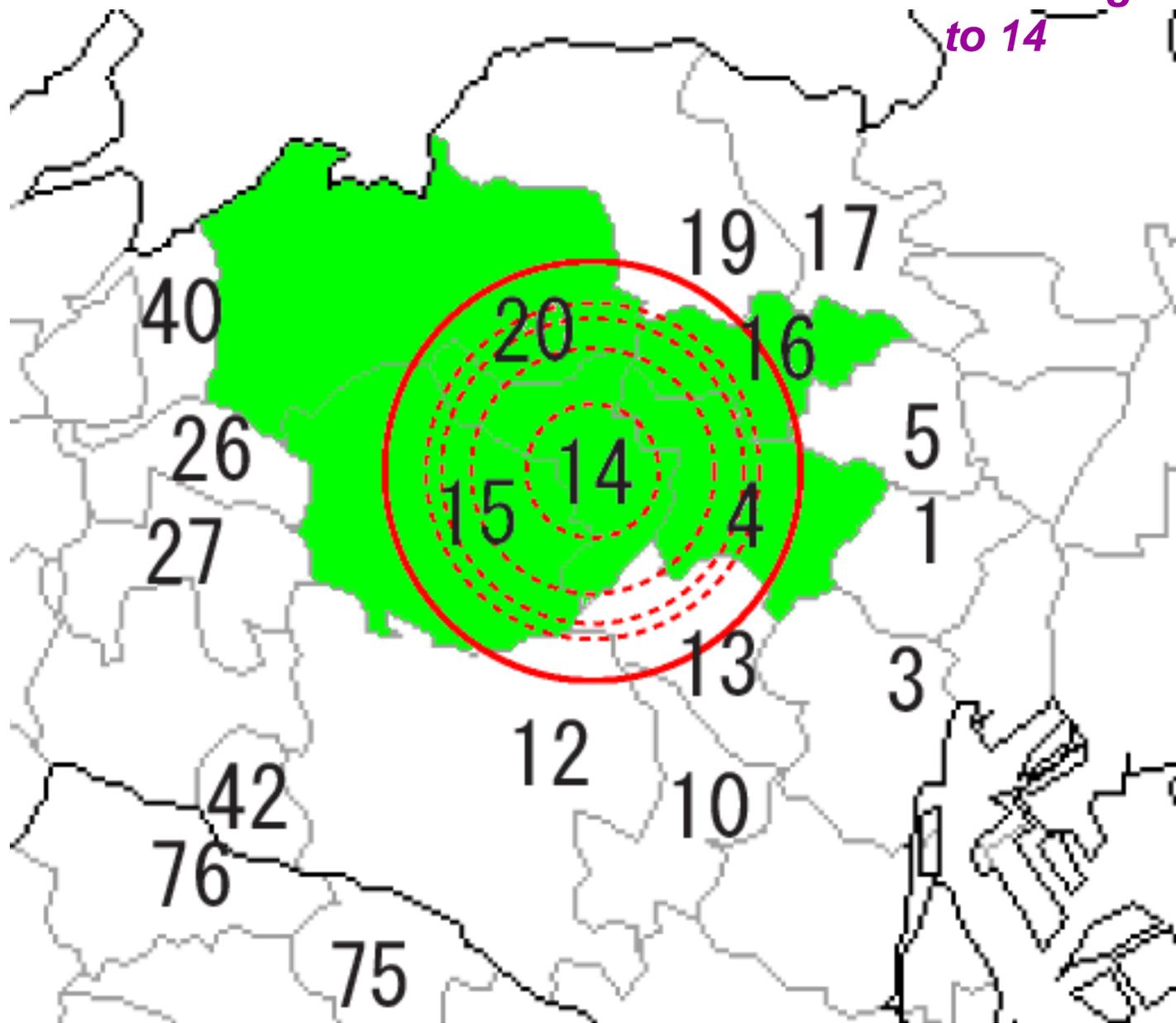
*20: 2nd-Nearest neighbour
to 14*

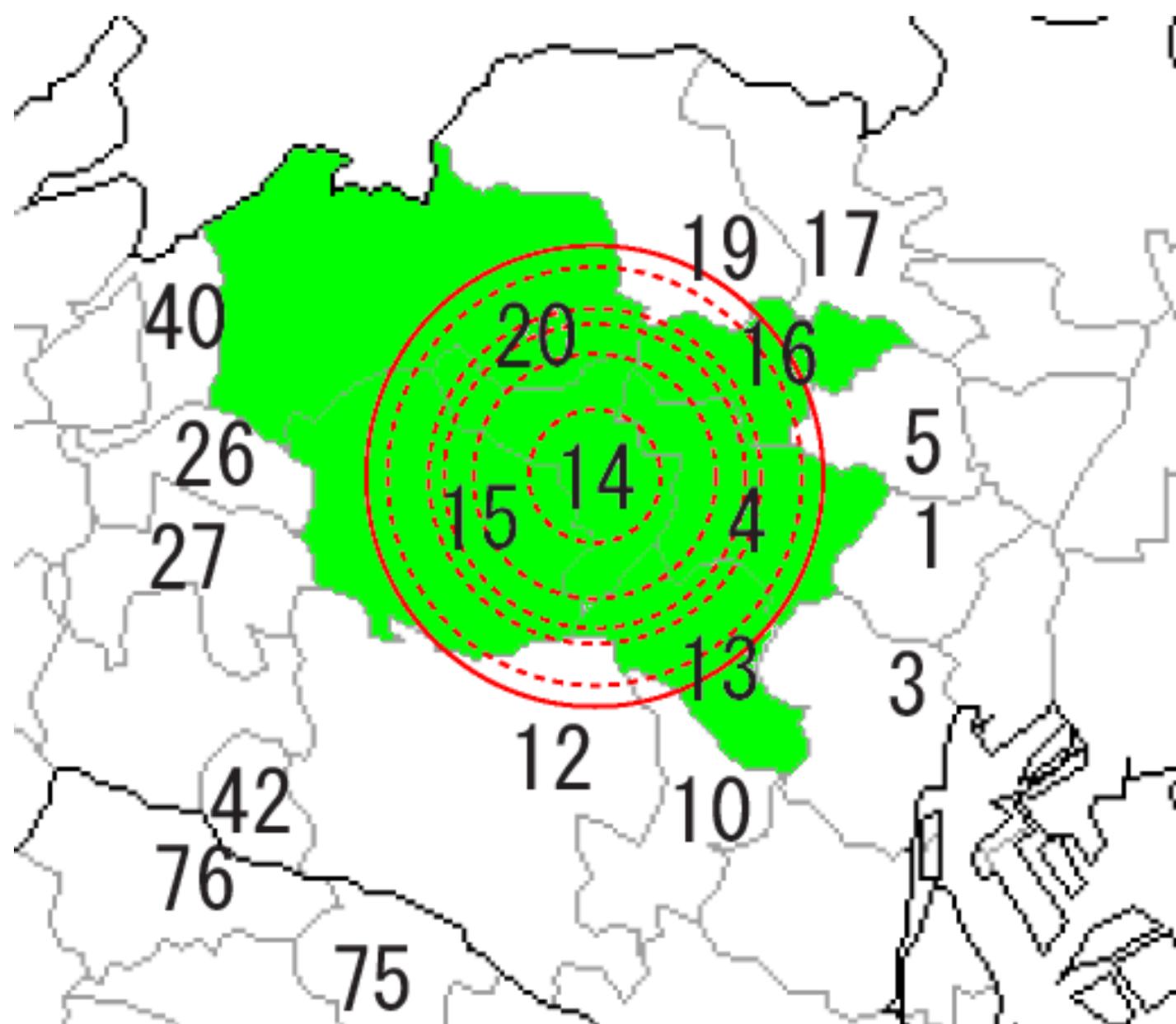


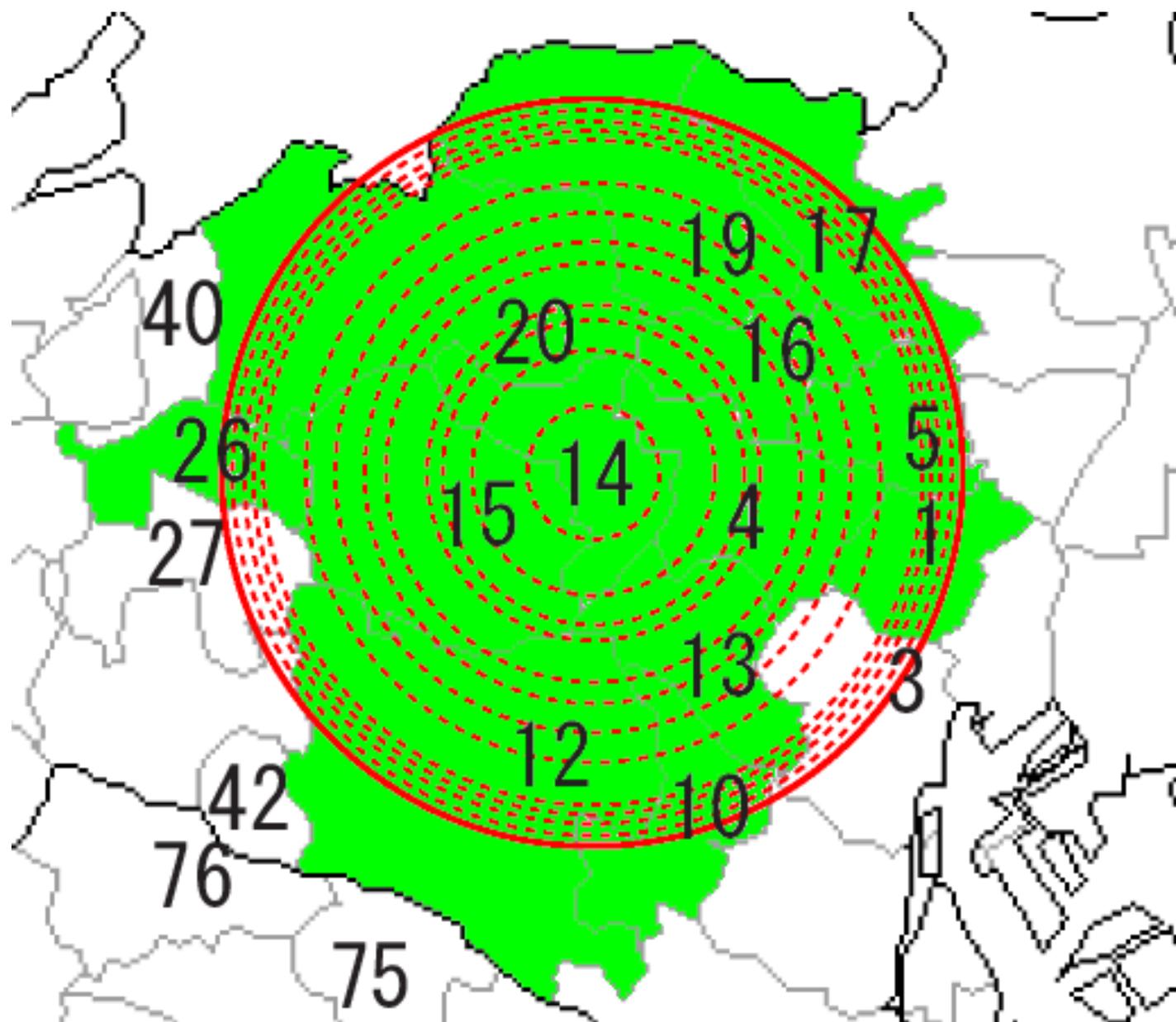
*4: 3rd-Nearest neighbour
to 14*

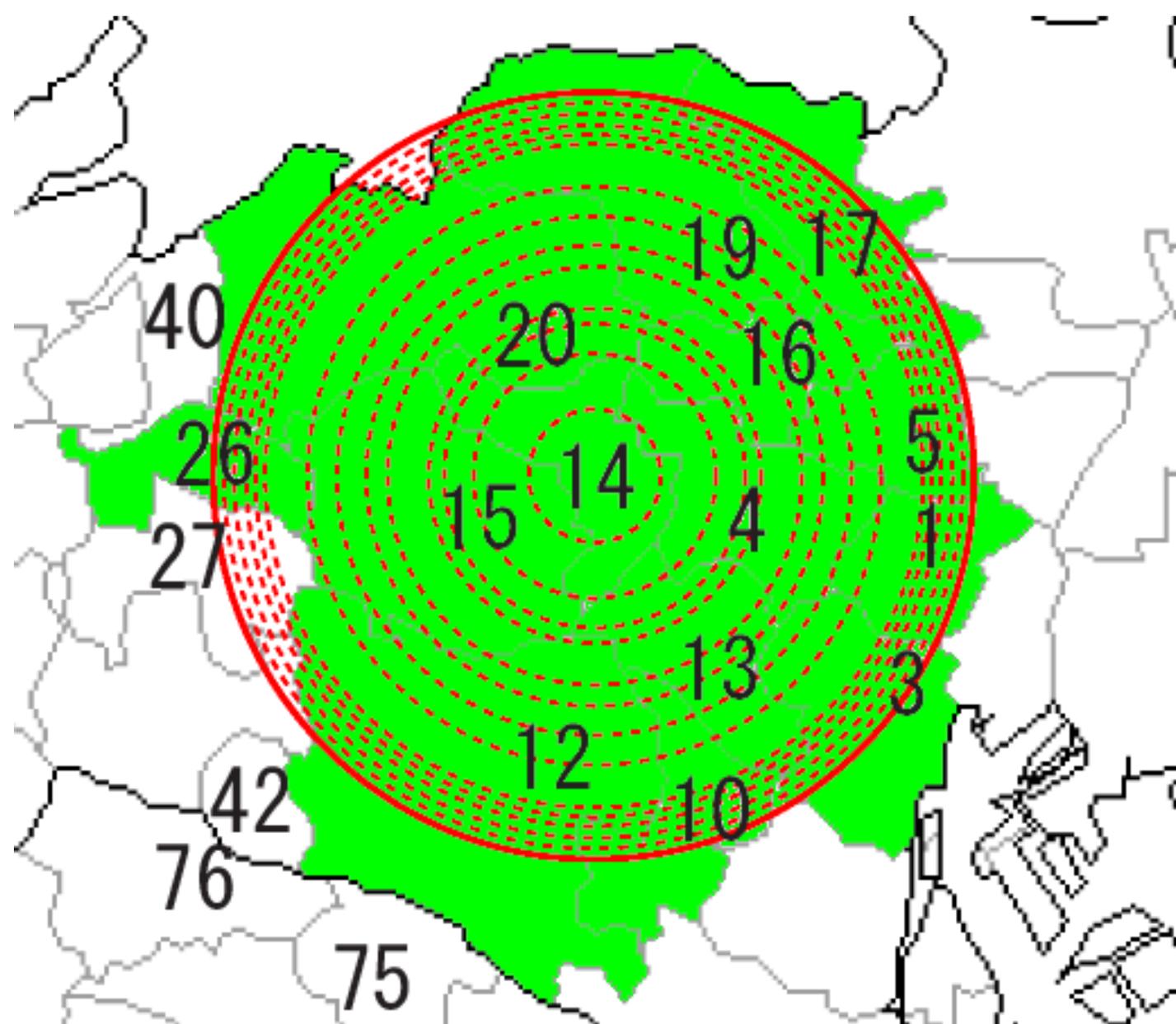


*16: 4th-Nearest neighbour
to 14*



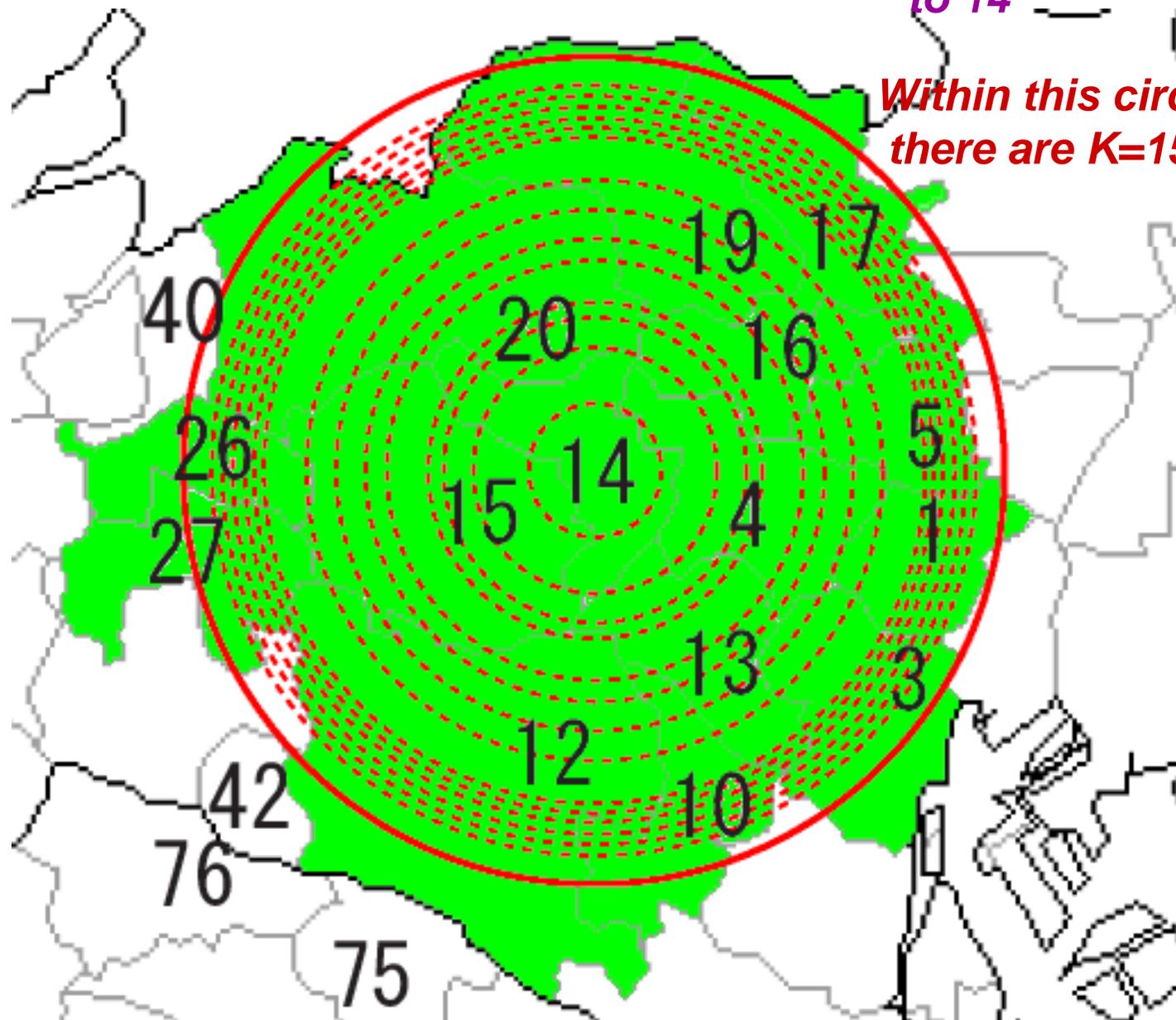






**27: 14th-Nearest neighbour
to 14**

**Within this circle,
there are $K=15$ regions**



Visual Disease Mapping System の開発

日本全国疾病地図

- ・ 都道府県別
- ・ 二次医療圏別
- ・ 市区町村別
 - a. SMR
 - b. Empirical Bayes SMR

疾病集積性の検定

- ・ **Kulldorff's Spatial Scan Test**
- ・ **Tango's Maximized Excess Events Test**



設定

計算方法 | 対象地域 | 作図凡例

計算方法

- SMR
- EBSMR
- Tangoの集積性
- Kulldorffの集積性

乱数設定

初期値: 56551 | 繰返数: 999

Input Data File

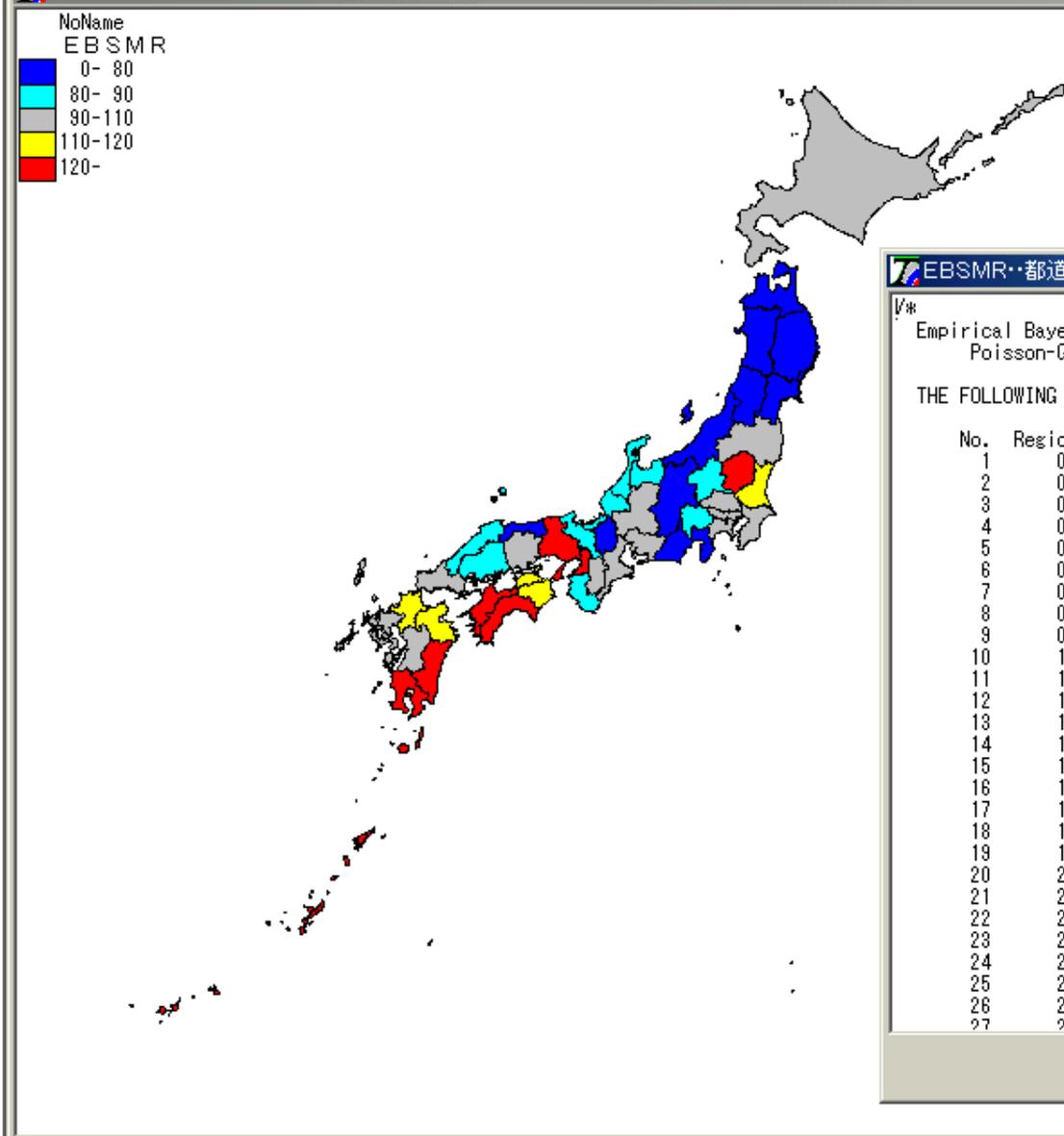
CTV_a_F.dat [参照]

データは死亡数と 期待死亡数 人口

Out Put File

CTV_a_F.SMR [参照]

処理開始(R) | キャンセル(O)



ぜん息死亡(女) 平成5 - 9年

EBSMR...都道府県...地域00... 計算結果

Empirical Bayes Estimator for SMR (SIR)
Poisson-Gamma model based MLE

THE FOLLOWING ESTIMATES ARE MLEs.

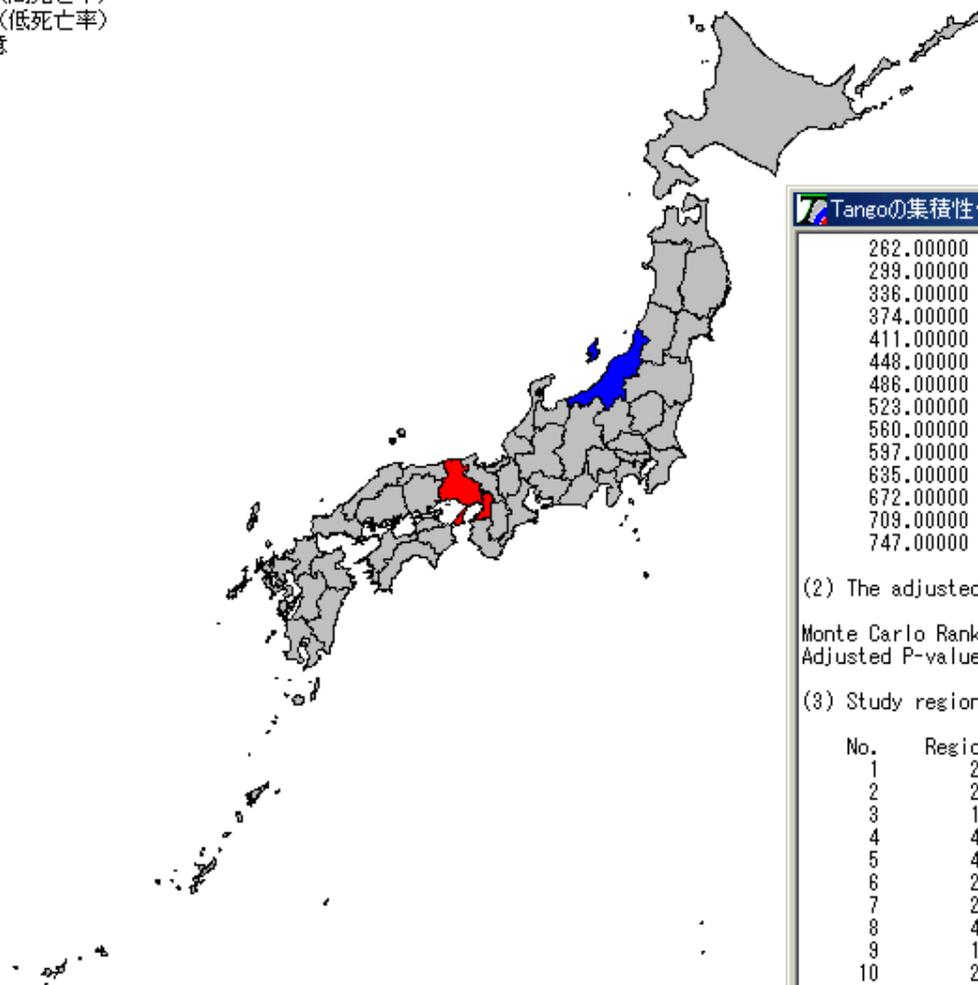
No.	Region	Observe	Expected	SMR	EBSMR	*/
1	01	591	608.699	97.092	97.126	*/
2	02	127	174.299	72.863	75.433	
3	03	135	183.888	73.414	75.810	
4	04	183	242.421	75.489	77.193	
5	05	105	166.109	63.212	66.918	
6	06	119	177.496	67.044	70.154	
7	07	242	265.295	91.219	91.700	
8	08	353	308.045	114.594	113.606	
9	09	268	211.756	126.561	124.144	
10	10	195	230.435	84.623	85.690	
11	11	562	529.890	106.060	105.777	
12	12	484	504.819	95.876	95.962	
13	13	1230	1156.968	106.312	106.176	
14	14	676	683.413	98.915	98.894	
15	15	198	337.312	58.699	60.878	
16	16	126	154.422	81.594	83.470	
17	17	125	146.731	85.190	86.726	
18	18	93	110.373	84.260	86.367	
19	19	101	114.069	88.543	89.961	
20	20	215	305.848	70.296	71.983	
21	21	222	233.232	95.184	95.417	
22	22	298	416.820	71.494	72.698	
23	23	591	619.187	95.448	95.532	
24	24	207	224.342	92.270	92.746	
25	25	97	137.941	70.320	73.800	
26	26	256	308.745	82.916	83.831	
27	27	992	811.865	122.188	121.619	

印刷 OK



NoName
Tangoの集積性P-value = 0.0010

- 有意 (高死亡率)
- 有意 (低死亡率)
- 否有意



ぜん息死亡(女) 平成5 - 9年

Tangoの集積性・都道府県・地域00 計算結果

262.00000	0.00000
299.00000	0.00000
336.00000	0.00000
374.00000	0.00000
411.00000	0.00000
448.00000	0.00000
486.00000	0.00000
523.00000	0.00000
560.00000	0.00000
597.00000	0.00000
635.00000	0.00000
672.00000	0.00000
709.00000	0.00000
747.00000	0.00000

(2) The adjusted P-value

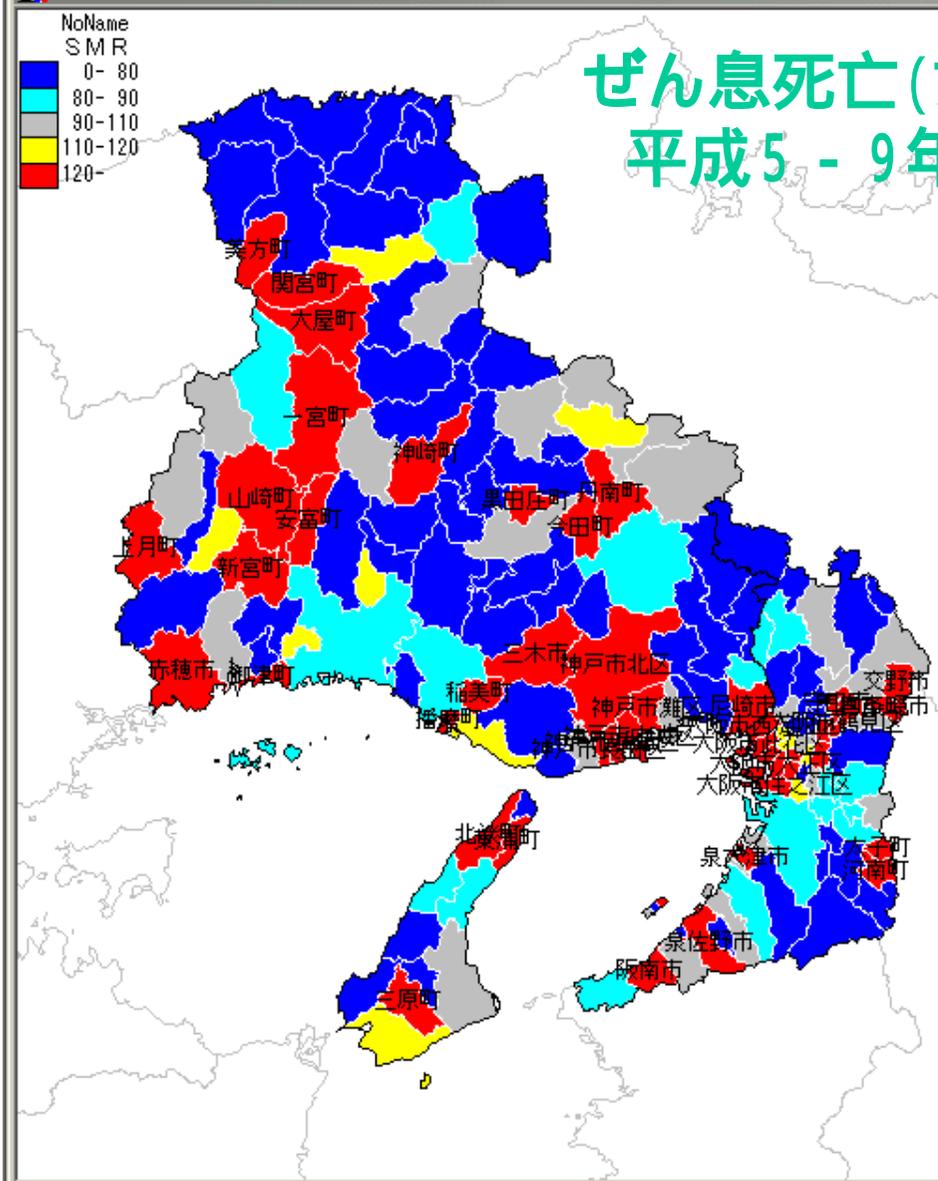
Monte Carlo Rank: 1/ 1000
Adjusted P-value: 0.0010000

(3) Study regions in the descending order of Percent cont.

No.	Region	Observed	Expected	SMR	Percent Cont	Std Per Cont
1	27	992	811.865	1.222	17.732	4.305
2	28	729	579.733	1.257	12.564	2.879
3	15	198	337.312	0.587	10.005	2.173
4	47	255	133.846	1.905	7.567	1.500
5	46	390	269.490	1.447	7.486	1.478
6	22	298	416.820	0.715	7.278	1.421
7	20	215	305.848	0.703	4.255	0.587
8	40	654	571.442	1.144	3.509	0.381
9	13	1230	1156.968	1.063	3.149	0.282
10	26	256	308.745	0.829	2.234	0.029
11	45	220	155.421	1.418	2.150	0.008

印刷

OK



ぜん息死亡(女) 平成5 - 9年

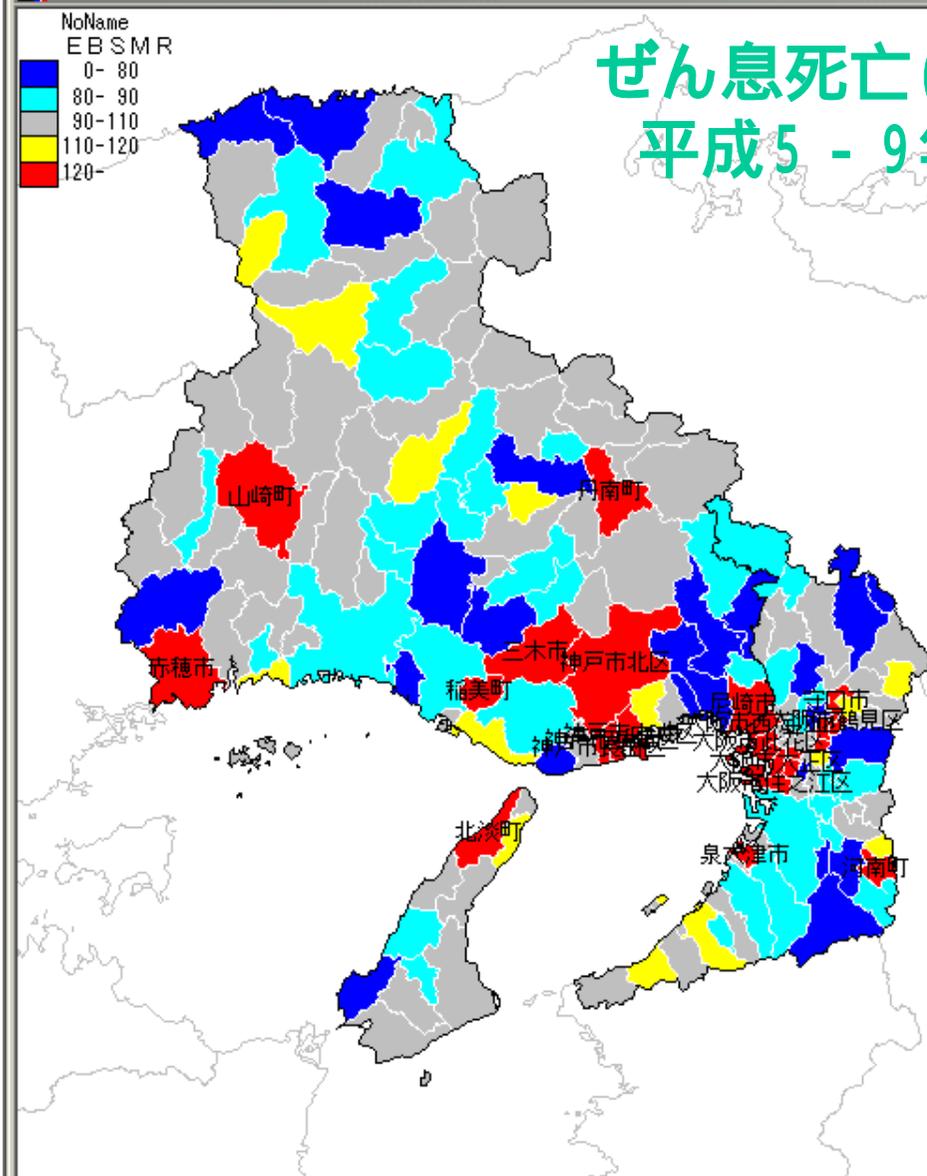
SMR市区町村地域27,28 計算結果

Empirical Bayes Estimator for SMR (SIR)
Poisson-Gamma model based MLE

THE FOLLOWING ESTIMATES ARE MLEs.

No.	Region	Observe	Expected	SMR	EBSMR	*/
1	27102	5	11.197	44.856	69.777	*/
2	27103	10	8.649	115.621	107.531	*/
3	27104	15	8.143	184.216	139.312	*/
4	27106	8	7.206	111.023	104.817	*/
5	27107	19	10.023	189.560	146.453	*/
6	27108	22	9.432	239.241	167.084	*/
7	27109	9	7.672	117.316	107.831	*/
8	27111	11	6.552	167.899	128.063	*/
9	27113	27	11.223	240.580	176.868	*/
10	27114	13	18.349	70.850	80.661	*/
11	27115	17	11.467	148.249	126.642	*/
12	27116	26	20.469	127.020	118.580	*/
13	27117	10	15.767	63.424	77.001	*/
14	27118	29	19.852	146.082	131.381	*/
15	27119	10	17.700	56.498	71.489	*/
16	27120	24	21.603	111.094	107.758	*/
17	27121	24	22.248	107.876	105.557	*/
18	27122	38	18.412	206.382	170.676	*/
19	27123	20	18.423	108.561	105.692	*/
20	27124	16	9.597	166.726	133.886	*/
21	27125	22	15.003	146.640	128.792	*/
22	27126	18	21.289	84.549	89.251	*/
23	27127	9	12.455	72.261	84.126	*/
24	27128	8	8.781	91.105	95.686	*/
25	27201	74	90.303	81.946	83.633	*/
26	27202	20	24.706	80.953	86.166	*/
27	27203	34	43.261	78.593	82.383	*/

印刷 OK



ぜん息死亡(女) 平成5 - 9年

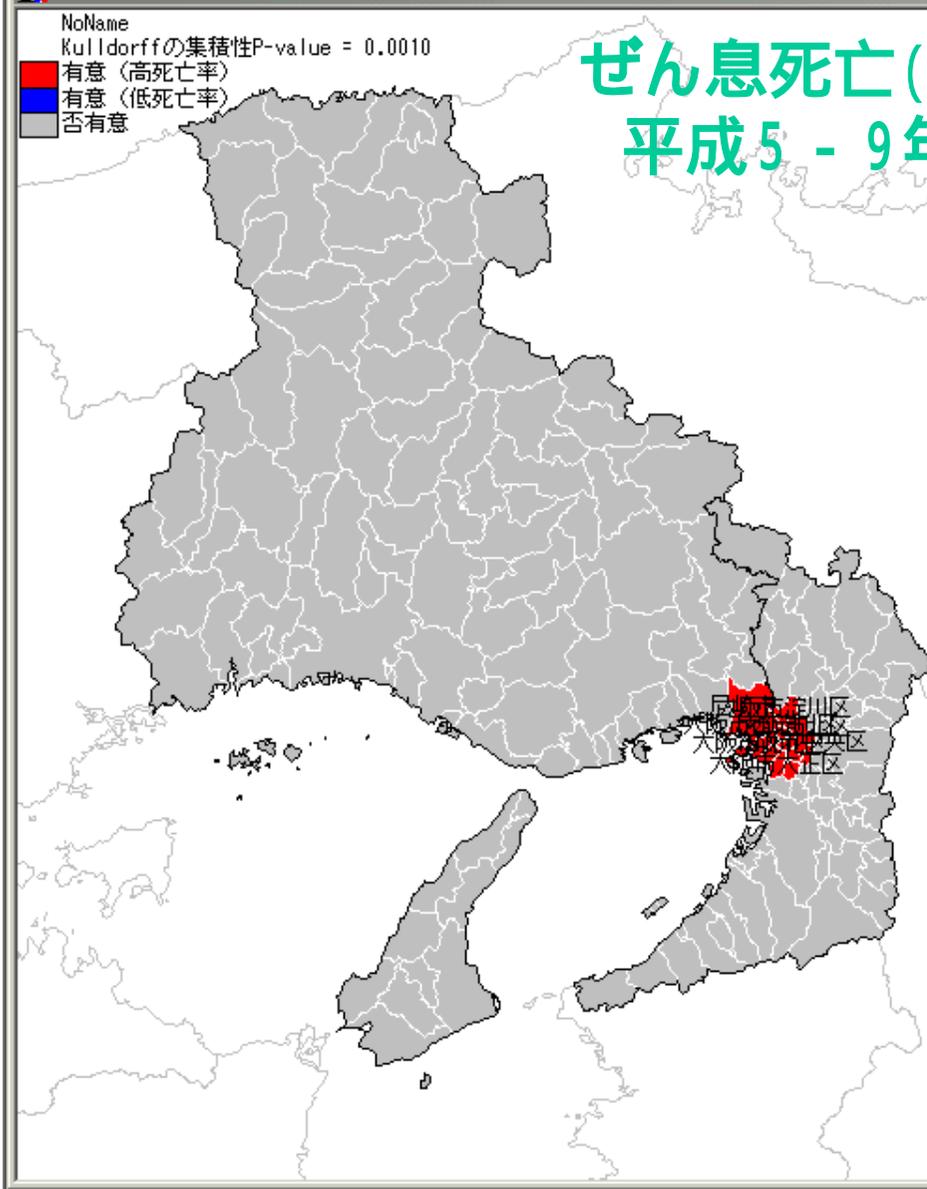
EBSMR・市区町村・地域:27,28・ 計算結果

Empirical Bayes Estimator for SMR (SIR)
Poisson-Gamma model based MLE

THE FOLLOWING ESTIMATES ARE MLEs.

No.	Region	Observe	Expected	SMR	EBSMR	*/
1	27102	5	11.197	44.656	89.777	*/
2	27103	10	8.649	115.621	107.531	
3	27104	15	8.143	184.216	139.312	
4	27106	8	7.206	111.023	104.817	
5	27107	19	10.023	189.560	146.453	
6	27108	22	9.432	233.241	167.084	
7	27109	9	7.672	117.316	107.831	
8	27111	11	6.552	167.899	128.063	
9	27113	27	11.223	240.580	176.868	
10	27114	13	18.349	70.850	80.661	
11	27115	17	11.467	148.249	126.642	
12	27116	26	20.469	127.020	118.580	
13	27117	10	15.767	63.424	77.001	
14	27118	29	19.852	146.082	131.381	
15	27119	10	17.700	56.498	71.489	
16	27120	24	21.603	111.094	107.758	
17	27121	24	22.248	107.876	105.557	
18	27122	38	18.412	206.382	170.676	
19	27123	20	18.423	108.561	105.692	
20	27124	16	9.597	166.726	133.886	
21	27125	22	15.003	146.640	128.792	
22	27126	18	21.289	84.549	89.251	
23	27127	9	12.455	72.261	84.126	
24	27128	8	8.781	91.105	95.686	
25	27201	74	90.303	81.946	83.633	
26	27202	20	24.706	80.953	86.166	
27	27203	34	43.261	78.593	82.383	

印刷 OK



V*
2001/11/06;13:32:38

Kulldorff's test statistic SaTScan for disease clusters

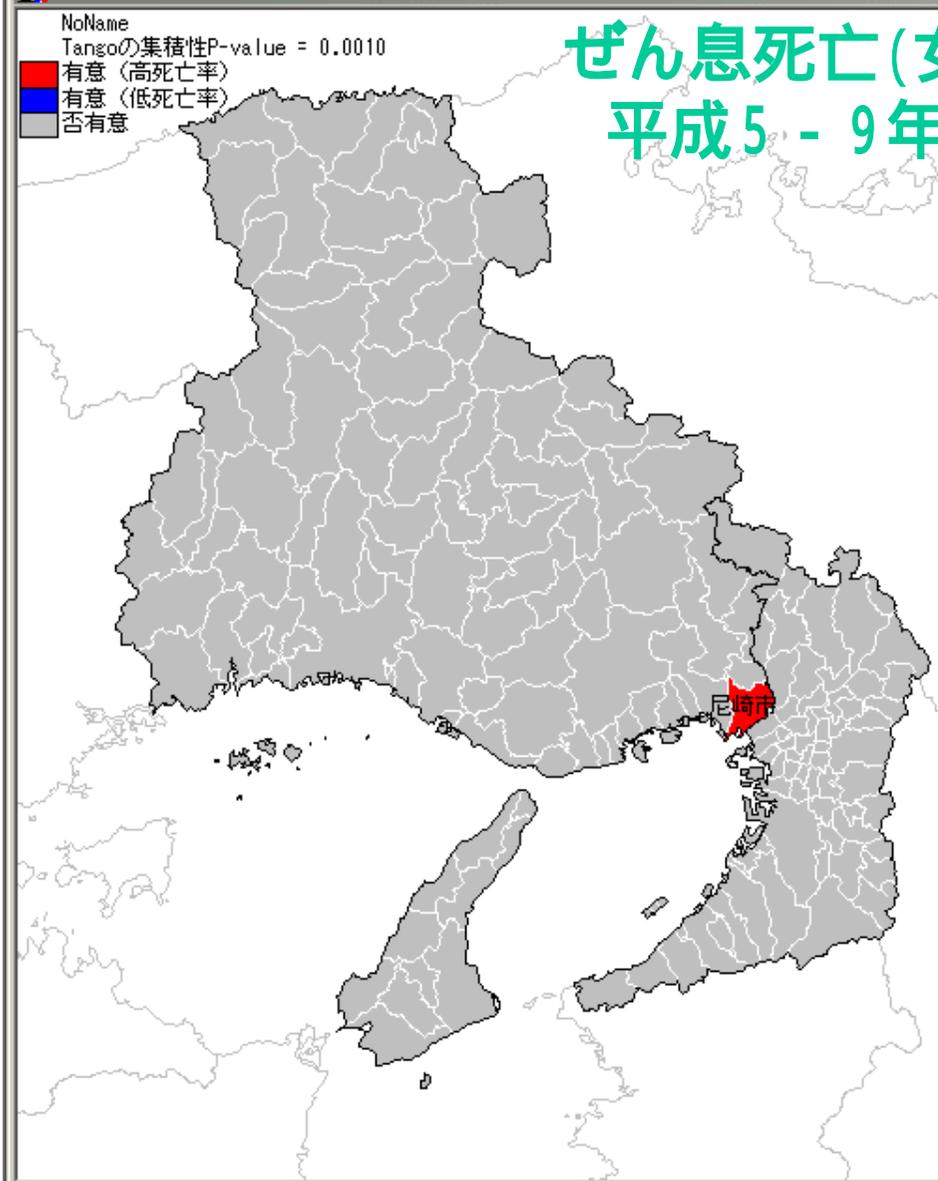
MOST LIKELY CLUSTER

Regions included	3:27104	5:27107	2:27103	9:27113	4:27106
Observed No. of cases ...	311				
Expected No. of cases ...	183.707				
SMR (SIR)	1.693				
Log likelihood ratio ...	41.85525				
Monte Carlo Rank	1/ 1000				
P-value	0.0010000				

2001/11/06 ;13:33:26

#/	Region	SMR
3	27104	1.693
5	27107	1.693
2	27103	1.693
9	27113	1.693
4	27106	1.693
6	27108	1.693
19	27123	1.693
8	27111	1.693
24	27128	1.693
23	27127	1.693
18	27122	1.693
7	27109	1.693
78	28202	1.693

印刷 OK



ぜん息死亡(女) 平成5 - 9年

Tangoの集積性・市区町村・地域27,28... 計算結果

17.00000	0.00000
20.00000	0.00000
23.00000	0.00000
25.00000	0.00000
28.00000	0.00000
31.00000	0.00000
34.00000	0.00000
37.00000	0.00000
39.00000	0.00000
42.00000	0.00000
45.00000	0.00000
48.00000	0.00000
50.00000	0.00000
53.00000	0.00000
56.00000	0.00000

(2) The adjusted P-value
Monte Carlo Rank: 1 / 1000
Adjusted P-value: 0.0010000

(3) Study regions in the descending order of Percent cont.

No.	Region	Observed	Expected	SMR	Percent Cont	Stnd Per Cont
1	28202	115	56.737	2.027	44.525	12.493
2	27122	38	18.412	2.064	5.032	1.260
3	27207	18	37.060	0.486	4.765	1.184
4	27201	74	90.303	0.819	3.486	0.820
5	27113	27	11.223	2.406	3.265	0.757
6	27227	43	57.548	0.747	2.776	0.618
7	28109	42	27.859	1.508	2.623	0.575
8	27205	21	33.903	0.619	2.184	0.450
9	27108	22	9.432	2.332	2.072	0.418
10	27206	20	7.793	2.566	1.954	0.385
11	28204	35	46.833	0.751	1.775	0.334
12	28105	26	16.376	1.588	1.215	0.174

印刷 OK

S-PLUSの新しいGIS機能として

- **標準の関数**として市区町村別の地図
- 距離(緯度、経度)が計算できる
- 隣接しているか否かの情報がわかる
(問題)市区町村合併が起こっている！

...