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H．知的財産権の出願・登録状況
（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

引用文献

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表1. 大阪府における進行度別罹患率の社会経済指標による格差：1993-2004年（時代変化）

		1993-1998													1999-2004										
		年齢調整罹患率（実測）					年齢調整罹患率（あてはめ）					格差(Q5-Q1)			年齢調整罹患率（実測）					年齢調整罹患率（あてはめ）					格差(Q5-Q1)			
		Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5		95% CI		Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5		95% CI		
男性	早期がん																										
	胃	24.4	26.2	24.3	24.8	22.7	25.5	25.0	24.4	23.9	23.4	−2.0	−3.6	−0.5	27.4	27.5	25.8	26.6	23.7	27.9	27.0	26.2	25.3	24.5	−3.4	−5	−1.8	
	大腸	19.5	19.5	19.8	19.8	18.0	19.9	19.6	19.3	19.0	18.7	−1.2	−2.6	0.2	25.0	22.0	21.9	23.0	20.3	24.0	23.2	22.4	21.5	20.7	−3.3	−4.8	−1.8	*
	肺	5.9	6.8	6.6	6.8	7.1	6.2	6.4	6.6	6.9	7.1	0.9	0.1	1.7	10.1	10.4	9.4	9.3	9.5	10.2	10.0	9.7	9.5	9.3	−0.9	−1.9	0.1	*
	前立腺	4.7	4.2	3.4	3.4	2.9	4.5	4.1	3.7	3.3	2.9	−1.6	−2.3	−1	12.3	9.4	9.1	9.0	6.5	11.6	10.4	9.2	8.0	6.8	−4.8	−5.8	−3.9	*
	進行がん																											
	胃	22.6	25.8	28.3	28.8	29.3	23.6	25.3	26.9	28.6	30.2	6.6	5	8.2	26.6	27.2	29.7	28.7	29.4	26.9	27.6	28.3	29.0	29.7	2.9	1.2	4.6	*
	大腸	13.5	15.3	17.8	18.3	18.0	14.1	15.3	16.5	17.7	18.9	4.8	3.5	6	18.3	20.4	20.4	22.1	20.7	19.1	19.7	20.3	21.0	21.6	2.5	1.1	3.9	*
	肺	24.5	27.3	28.5	30.9	32.6	24.8	26.8	28.8	30.8	32.8	8.0	6.3	9.7	32.2	32.8	34.3	35.5	37.6	31.8	33.1	34.5	35.9	37.2	5.4	3.6	7.3	*
	前立腺	4.1	4.4	4.0	3.8	3.9	4.3	4.2	4.0	3.9	3.8	−0.5	−1.1	0.2	6.3	5.5	5.1	5.4	5.0	5.9	5.7	5.4	5.2	4.9	−1.0	−1.8	−0.3	
女性	早期がん																											
	胃	8.8	9.5	10.1	10.0	10.2	9.0	9.4	9.7	10.1	10.4	1.4	0.5	2.4	9.6	9.0	9.0	9.2	10.1	9.1	9.2	9.4	9.5	9.6	0.5	−0.4	1.4	
	大腸	10.0	9.4	10.9	11.0	9.6	10.0	10.1	10.1	10.2	10.2	0.2	−0.7	1.1	12.8	11.6	11.3	12.3	11.2	12.3	12.0	11.8	11.6	11.4	−0.9	−1.9	0.1	
	肺	2.4	1.9	2.5	2.6	2.7	2.1	2.3	2.4	2.6	2.7	0.6	0.1	1.1	4.4	4.0	4.3	4.3	4.2	4.3	4.2	4.2	4.2	4.2	−0.1	−0.6	0.5	
	乳房	19.4	19.0	19.6	21.2	18.6	19.4	19.5	19.5	19.6	19.6	0.2	−1.3	1.6	24.5	22.8	23.3	24.4	24.0	23.6	23.7	23.8	23.9	23.9	0.3	−1.3	1.9	
	子宮頸	7.3	7.9	8.7	8.7	9.2	7.4	7.9	8.4	8.8	9.3	1.9	0.9	2.9	6.8	7.8	6.9	8.0	7.9	6.9	7.2	7.4	7.7	8.0	1.0	0.1	2	
	進行がん																											
	胃	9.9	11.8	12.3	11.9	12.7	10.5	11.1	11.7	12.3	12.9	2.3	1.3	3.4	9.1	11.9	10.8	11.9	11.8	9.9	10.5	11.1	11.6	12.2	2.3	1.3	3.2	
	大腸	9.2	11.1	11.5	12.0	12.1	9.8	10.4	11.1	11.8	12.5	2.7	1.8	3.7	11.5	12.2	13.2	13.7	13.4	11.8	12.3	12.8	13.3	13.8	2.1	1	3.1	
	肺	6.7	7.9	8.9	9.2	10.9	6.8	7.7	8.7	9.7	10.6	3.8	2.9	4.7	8.8	9.7	9.8	10.1	11.2	8.9	9.4	9.9	10.4	10.9	2.0	1.1	2.9	*
	乳房	13.8	14.5	14.6	15.2	16.0	13.8	14.3	14.8	15.3	15.8	2.1	0.8	3.3	13.9	15.0	15.9	17.6	16.4	14.2	15.0	15.7	16.5	17.3	3.1	1.8	4.3	
	子宮頸	2.5	2.8	3.7	3.4	4.2	2.5	2.9	3.3	3.7	4.1	1.6	1	2.2	2.1	2.9	3.0	2.9	3.5	2.3	2.6	2.9	3.2	3.4	1.1	0.6	1.7	

年齢調整罹患率は人口10万人対

*は診断時期間で格差の大きさに統計的有意に変化があったもの（$p<0.05$）

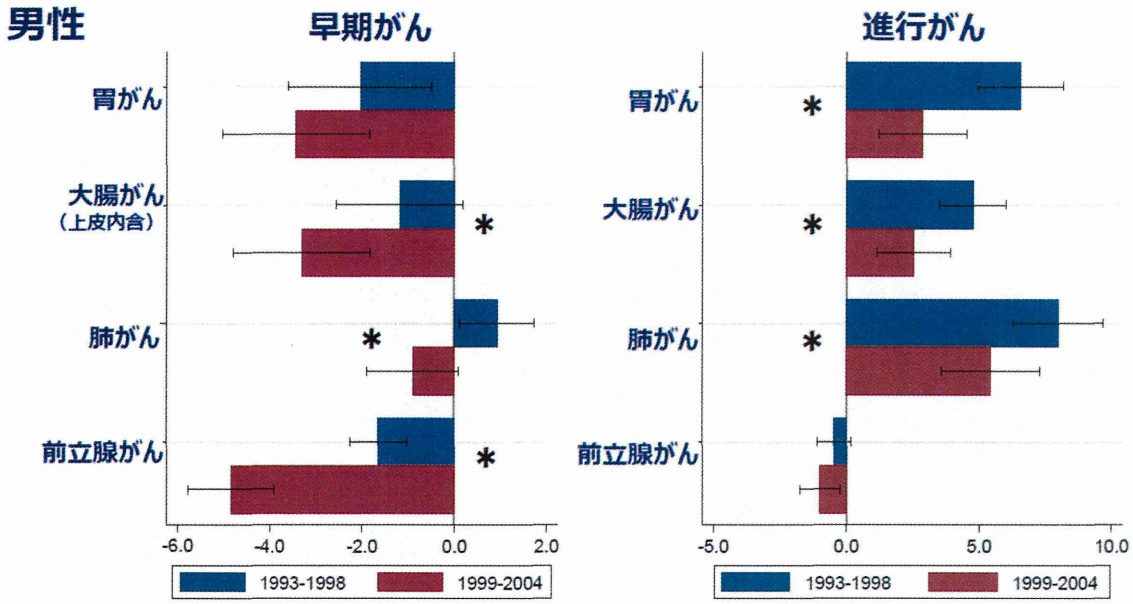

図 1. 大阪府男性における部位別進行度別がん罹患率の格差（Q5 の年齢調整罹患率と Q1 の年齢調整罹患率）：1993－1998 年／1999－2004 年

＊は、診断時期間で格差が統計的有意に変化した部位（p<0.05）

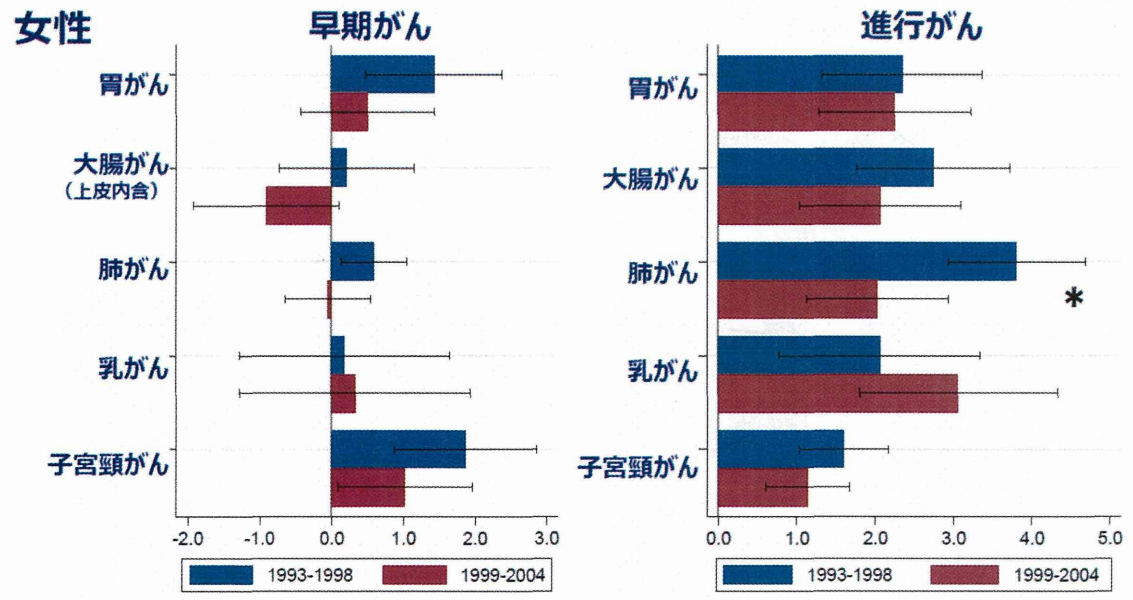

図 2. 大阪府女性における部位別進行度別がん罹患率の格差（Q5 の年齢調整罹患率と Q1 の年齢調整罹患率）：1993－1998 年／1999－2004 年

＊は、診断時期間で格差が統計的有意に変化した（p<0.05）

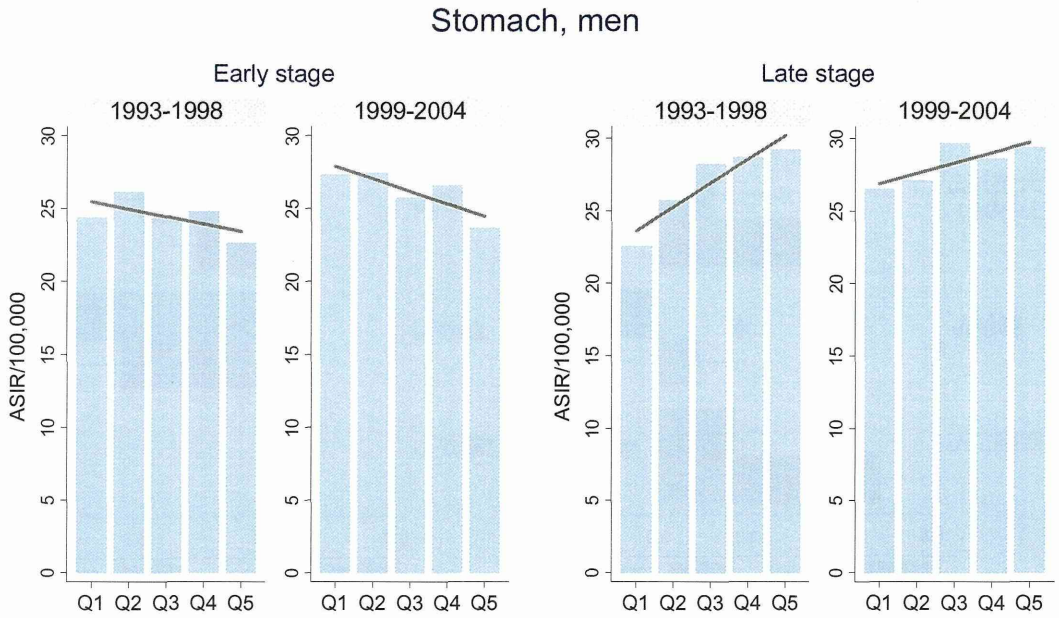

図 3. 大阪府胃がん男性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

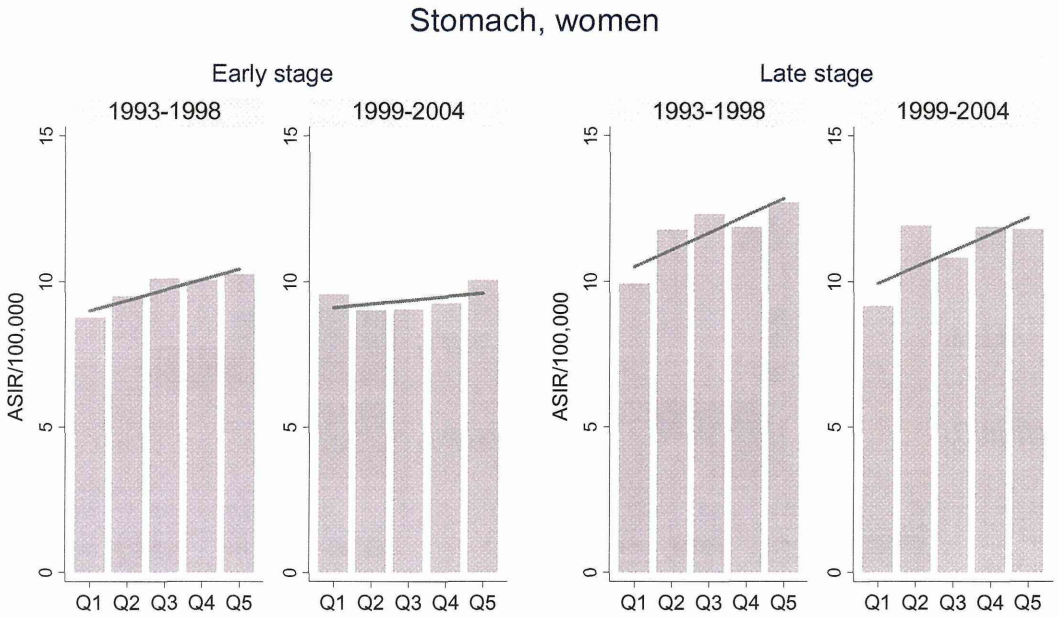

図 4. 大阪府胃がん女性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

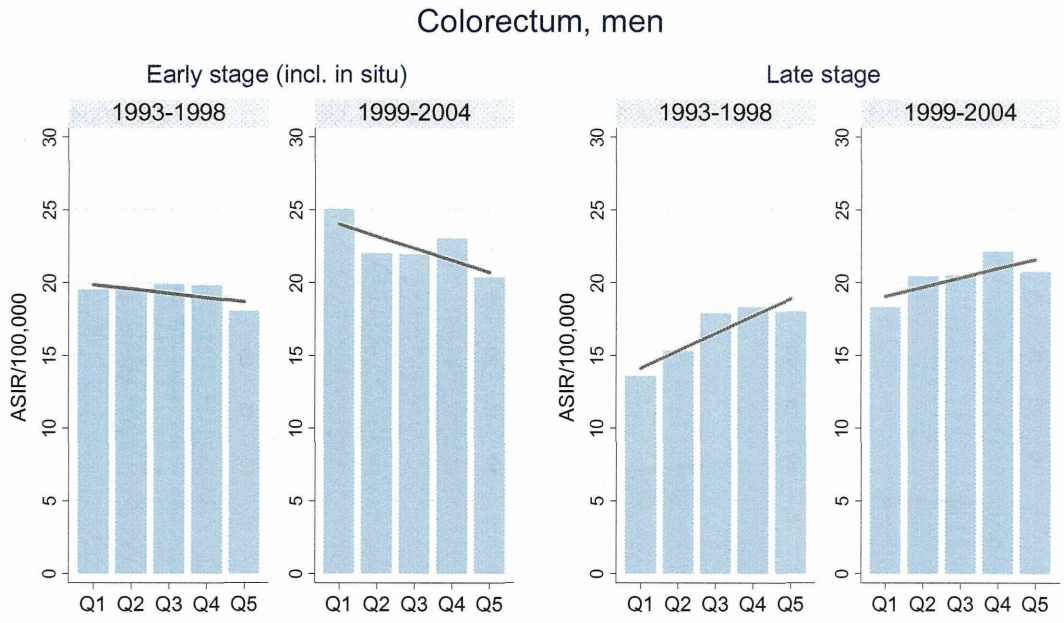

図 5. 大阪府大腸がん男性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

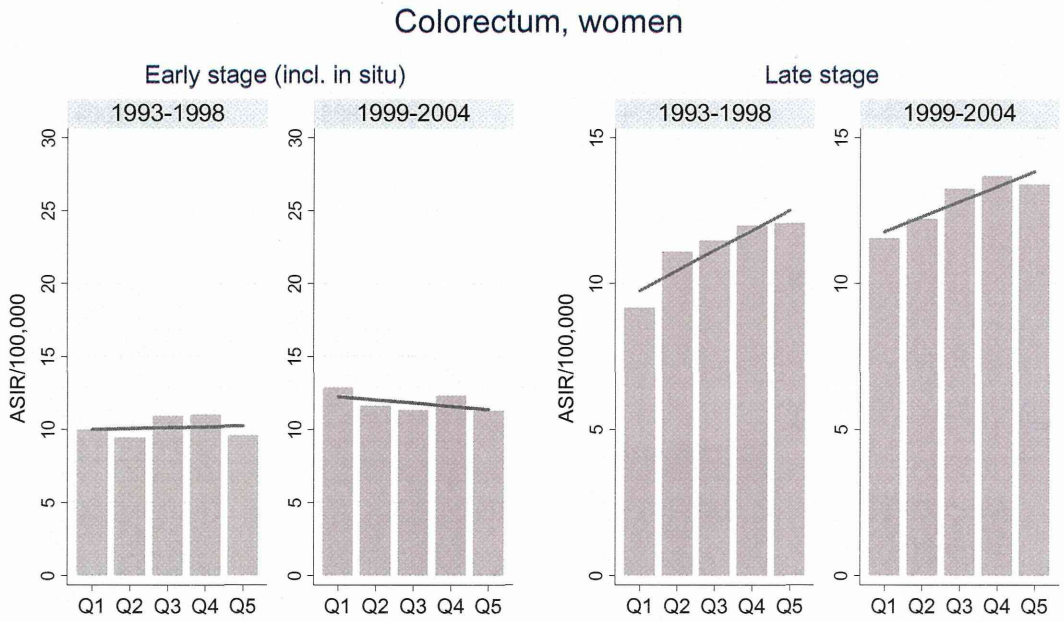

図 6. 大阪府大腸がん女性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

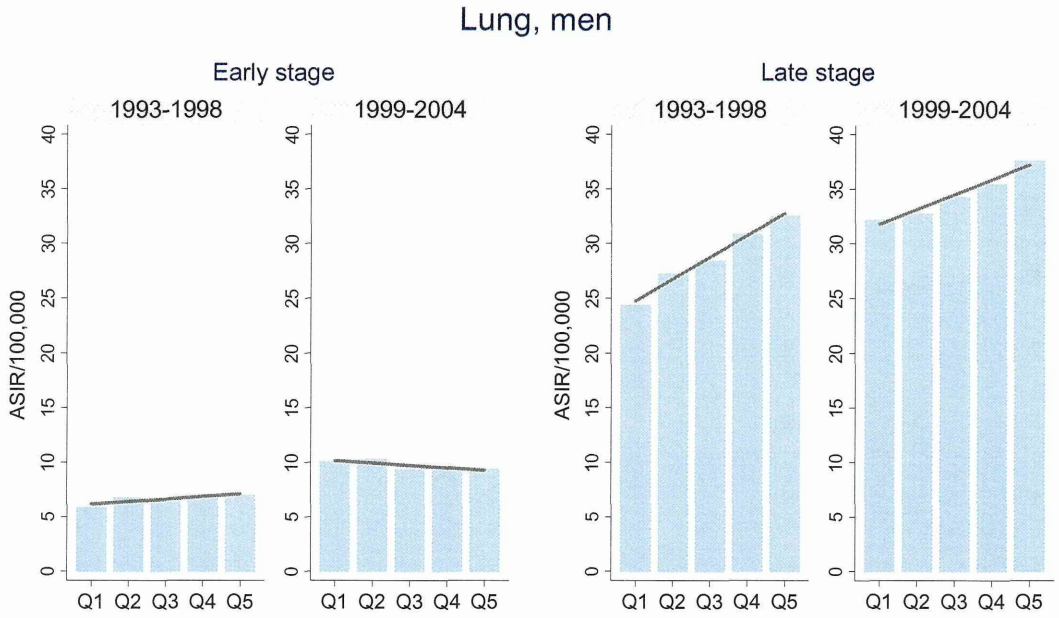

図 7. 大阪府肺がん男性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

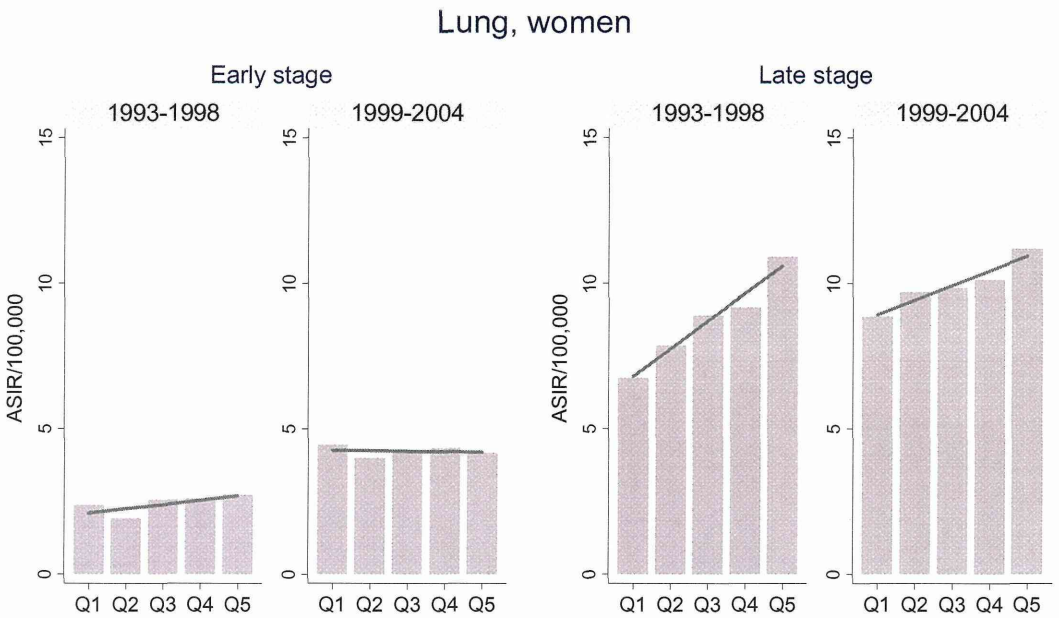

図 8. 大阪府肺がん女性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

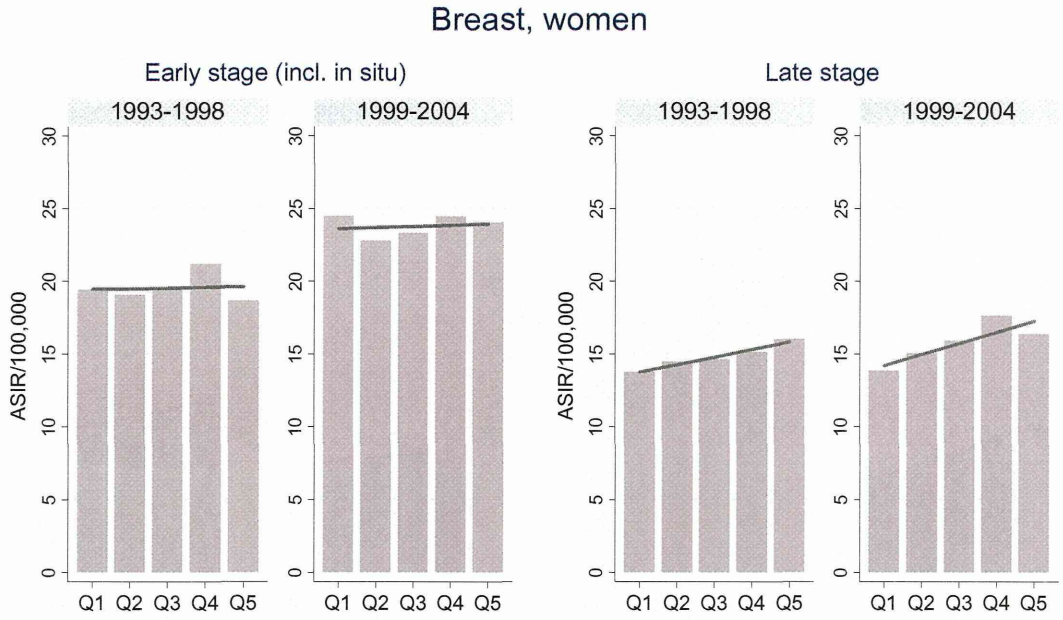

図 9. 大阪府乳がん女性の ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

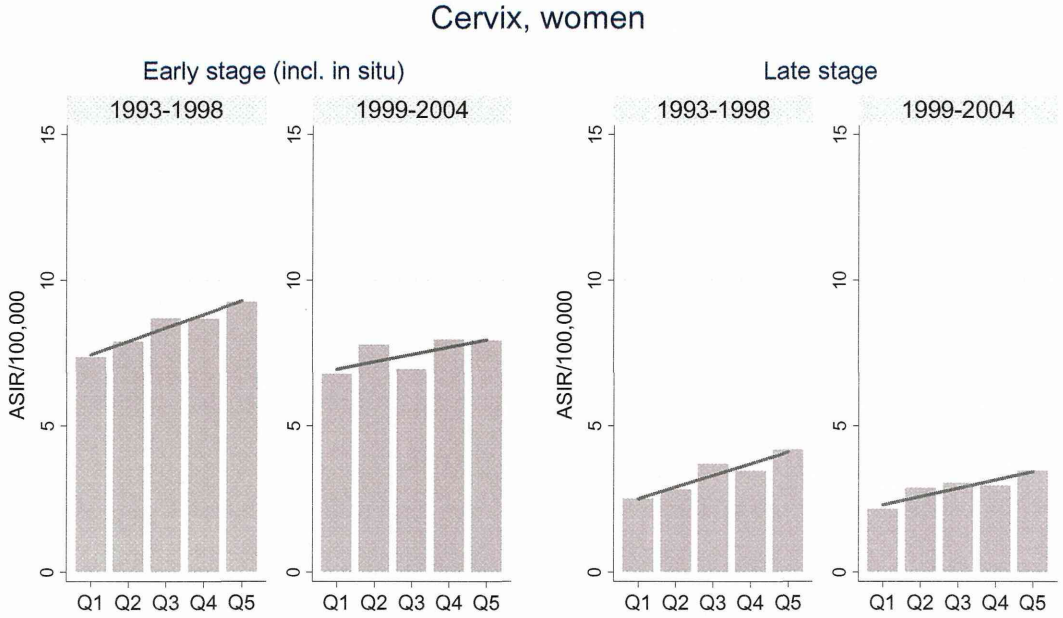

図 10. 大阪府子宮頸がんの ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

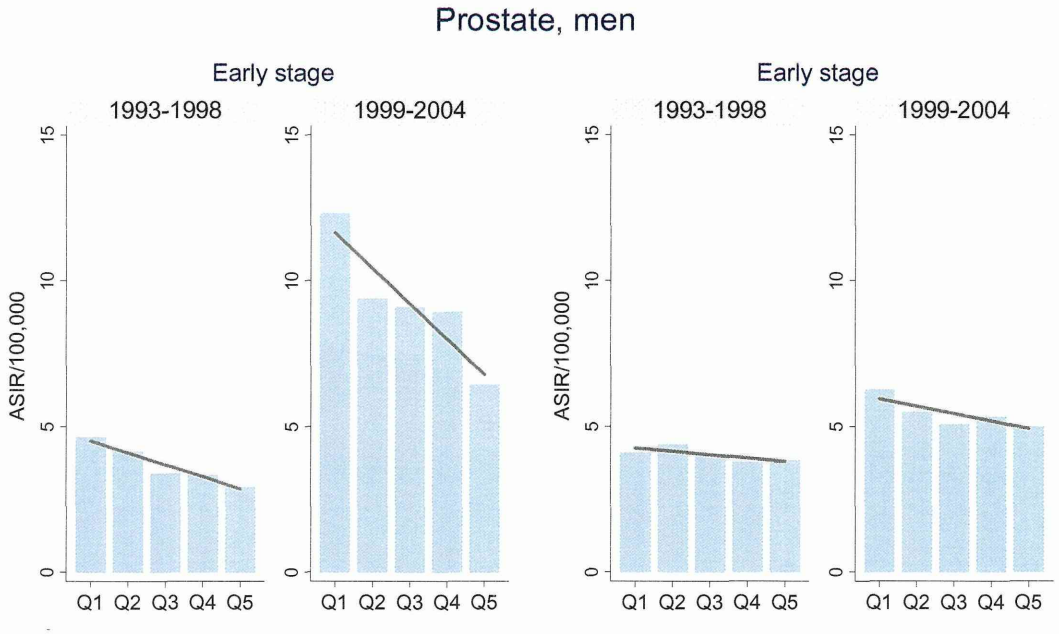

図 11. 大阪府前立腺がんの ADI5 分位別進行度別年齢調整罹患率：1993～1998 年／1999～2004 年（直線は分散重み付き最小二乗法によるあてはめ）

III. 研究成果に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ito Y, Nakaya T, Ioka A, Nakayama T, Tsukuma H, Uehara S, Sato KK, Endo G, Hayashi T	Investigation of Spatial Clustering of Biliary Tract Cancer Incidence in Osaka, Japan: Neighborhood Effect of a Printing Factory.	J Epidemiol			2016 In press
Kinoshita F, Ito Y, Nakayama T	Trends in lung cancer incidence rates by histological type in 1975-2008: a population-based study in Osaka, Japan.	J Epidemiol			2016 In press
伊藤ゆり，中山富雄	肺がん生存率の国際比較	肺癌	55	266-272	2015
中谷友樹・埴淵知哉	健康の社会格差と地域格差	地理	61(1)	51-57	2016

IV. 研究成果の刊行物・別刷

Advance Publication by J-STAGE

J Epidemiol 2016
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Original Article

Investigation of Spatial Clustering of Biliary Tract Cancer Incidence in Osaka, Japan: Neighborhood Effect of a Printing Factory

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ABSTRACT

Background: In 2013, an unusually high incidence of biliary tract cancer among current or former workers of the offset color proof printing department of a printing company in Osaka, Japan, was reported. The purpose of this study was to examine whether distance from the printing factory was associated with incidence of biliary tract cancer and whether incident biliary tract cancer cases clustered around the printing factory in Osaka using population-based cancer registry data.

Methods: We estimated the age-standardized incidence ratio of biliary tract cancer according to distance from this printing factory. We also searched for clusters of biliary tract cancer incidence using spatial scan statistics.

Results: We did not observe statistically significantly high or low standardized incidence ratios for residents in each area categorized by distance from the printing factory for the entire sample or for either sex. The scan statistics did not show any statistically significant clustering of biliary tract cancer incidence anywhere in Osaka prefecture in 2004–2007.

Conclusions: There was no statistically significant clustering of biliary tract cancer incidence around the printing factory or in any other areas in Osaka, Japan, between 2004 and 2007. To date, even if some substances have diffused outside this source factory, they do not appear to have influenced the incidence of biliary tract cancer in neighboring residents.

Key words: standardized incidence ratio; biliary tract cancer; spatial clusters; cancer registry

INTRODUCTION

In 2013, an unusually high incidence of biliary tract cancer among young current or former workers at the offset color proof department of a printing company in Osaka, Japan, was reported.[1] In 2014, clinical findings of 17 patients who had worked at this printing factory and had a diagnosis of biliary tract cancer between 1996 and 2012 were reported.[2–4] Standardized incidence ratios (SIRs) of biliary tract cancer for workers in this offset color proof printing factory, using the national incidence level as a reference, have been reported to be more than 1000.[5] Exposure to 1,2-dichloropropane or both 1,2-dichloropropane and dichloromethane at printing factories has been reported to be associated with risk of biliary tract cancer.[2,6] If some substances have diffused outside this factory, it is important to establish whether this contamination has influenced the incidence of biliary tract cancer in neighboring residents.

Therefore, we examined whether distance from the printing factory was associated with the incidence of biliary tract cancer and whether there was any clustering of biliary tract cancer incidence around this printing factory in Osaka using data from a population-based cancer registry. A cluster was defined as an area where an unusually high incidence of disease occurs compared with the incidence in the whole study region.

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METHODS

Data sources

To examine the association of distance from the printing factory with biliary tract cancer incidence, we used incidence data[7] and population data[8] by small administrative unit, and compared data with the standard incidence rate[7] in Osaka, Japan. Osaka Prefecture is located at the approximate center of Japan and has the third largest population (8.8 million) of any prefecture in Japan (eFigure 1A). Osaka Prefecture has 43 municipalities, comprising 33 cities, nine towns, and one village. Osaka City has 24 wards (eFigure 1B). The printing factory is located in Osaka City (eFigure 1B).

Incidence data of biliary tract cancer among residents in Osaka prefecture from 2004 to 2007 was obtained from the Osaka Cancer Registry.[7] Incidence of biliary tract cancer was identified using codes C22.1 and C24.0 of the International Classification of Diseases, 10th revision. The number of observed incident cases was calculated by sex and patient address using the small geographic area called "Cho-Aza level" in Japan. The Cho-Aza level, which is much smaller than a municipality and a prefecture, is one of the elements of the address system in Japan (eFigure 1B). Of 17 patients who had worked at this factory and had a diagnosis of biliary tract cancer, three incident cases diagnosed with biliary tract cancer between 2004 and 2007 were excluded from the analysis to distinguish occupational exposure from environmental exposure. This study was approved by the data usage committee of the Osaka Cancer Registry of the Osaka Medical Center for Cancer and Cardiovascular Diseases in September 2012 (approval ID: No. 12-0007).

Population data by sex, 5-year age group, and Cho-Aza level in Osaka were obtained from the 2005 National Census to calculate the expected number of incident cases of biliary tract cancer for the Cho-Aza level.[8]

To control for differences in age distribution among areas, we used SIRs. The SIRs of biliary tract cancer by sex and 5-year age group were calculated using whole cases and age-specific population in Osaka in 2004–2007 (see eTable 1). We limited the age range to 0 to 84 years for all analyses because data for the over-85-year age group showed unstable statistical results in the small area that we used in this study.

Statistical analysis

Relationship between distance from the printing factory and biliary tract cancer incidence

We calculated SIRs using the indirect method to control for differences in age distribution among areas categorized by distance from the printing factory (<1.0 km, 1.0 to <2.0 km, 2.0 to <3.0 km, 3.0 to <4.0 km, 4.0 to <5.0 km, and ≥5.0 km). The expected number of cases in each categorized area was obtained from the sum of the products of population in each area and standard incidence rate of biliary tract cancer by 5-year age group and sex in Osaka in 2004–2007. The 95% confidence intervals of SIR were calculated using Fisher's exact method by assuming a Poisson process.[9] Distance from the printing factory was used as a categorical variable because the number of incident cases was not sufficient to obtain stable results using distance as a continuous variable. The analysis was performed using the statistical package Stata ver. 13.1. (StataCorp, College Station, TX, USA).[10]

Clustering of biliary tract cancer incidence

We also searched for clusters of biliary tract cancer incidence in Osaka using spatial scan statistics (Poisson model). We used SaTScan v.9.1.1 (Martin Kulldorff, Boston, MA, USA), which can detect clusters of infectious and chronic diseases, vectors, and risk of diseases.[11] A disease cluster is defined as an area where an unusually high incidence of disease occurs compared with the incidence in the whole of the study region. Recently, Kulldorff's SaTScan[11] has become the most widely used tool for detecting disease clusters in epidemiological studies, especially for cancer control studies.[12–18] A summary of the spatial scan statistics (Poisson model) to identify clusters is shown in eAppendix 1.[12,17,19,20]

To detect significant clusters, a large number of circular windows with varied radii were generated. Each circle window had a different radius and scanned all points of the area. We used the Cho-Aza level as the smallest geographical area to detect clusters. The spatial scan statistics, which were calculated as likelihood ratios, were calculated for all circles. This method, which focuses on the maximum likelihood ratio, can avoid the need for multiple testing to identify clusters. To obtain the *P*-value for the statistically significant test and to define the cluster, we generated 999 replications of a Monte Carlo simulation.

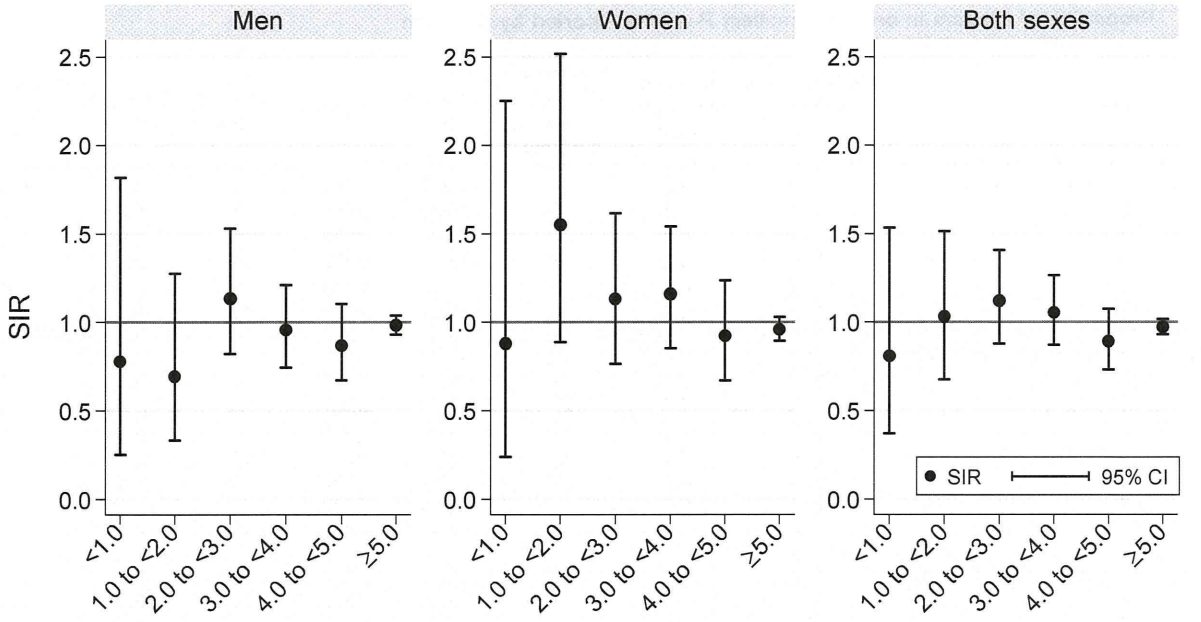
We set the maximum spatial cluster size as 2.0 km to confirm the environmental exposure of chemical substances because, even in the case of asbestos exposure, which can be diffused over a longer distance than chemical substances, the maximum environmental exposure was reported as 2.2 km.[21] To identify the cluster, we allowed overlapping with the most likely cluster.

RESULTS

The 2492 cases of biliary tract cancer in Osaka prefecture, Japan, in 2004–2007 included 1528 men and 964 women. The crude incidence rate per 100 000 person-years was 7.24 (9.07 in men and 5.48 in women). The age-standardized incidence rate per 100 000 person-years was 4.37 (5.94 in men and 3.06 in women). Higher incidence rates were observed in the older age group (eTable 1). More detailed descriptive epidemiology of biliary tract cancer in Osaka prefecture has been reported elsewhere.[22]

Relationship between distance from the printing factory and biliary tract cancer incidence

The aim of the first set of the analysis was to determine whether the distance from the printing factory was associated



	Men						Women						Both sexes					
Obs.	5	10	43	69	66	1276	4	16	30	47	44	786	9	26	73	116	110	2062
Exp.	6.4	14.4	37.9	72.2	76.1	1297.9	4.5	10.3	26.5	40.5	47.8	819.0	11.1	25.2	65.2	110.1	123.4	2119.6
SIR	0.78	0.69	1.14	0.96	0.87	0.98	0.88	1.55	1.13	1.16	0.92	0.96	0.81	1.03	1.12	1.05	0.89	0.97

Figure 1. Standardized incidence ratios of residents according to the distance from the printing factory in 2004–2007 in Osaka, Japan.
CI, confidence interval; Exp, expected number of biliary tract cancer cases; Obs, observed number of biliary tract cancer cases; SIR, standardized incidence rate.

with biliary tract cancer incidence. As shown in Figure 1, we did not observe statistically significantly high or low SIRs of residents in any areas categorized by distance from the printing factory.

Clustering of biliary tract cancer incidence

We have listed the properties of the clusters in increasing order of *P*-value reported by SaTScan for both sexes and by sex in Table 1. According to the scan statistics analysis for both sexes, the most likely cluster was located 4.7 km from the printing factory, but the *P*-value was 0.217 and not statistically significant. The most likely cluster for men was located 8.2 km from the printing factory, and the most likely cluster for women was located 11.7 km from the printing factory; neither cluster was statistically significant. In addition, the radiuses of those clusters were small, and the printing factory was not located inside the clusters. The scan statistics did not show any statistically significant clustering of biliary tract cancer incidence anywhere in Osaka prefecture in 2004–2007.

DISCUSSION

Our study demonstrated that distance from the printing factory was not associated with incidence of biliary tract cancer and that there was no statistically significant clustering of biliary tract cancer incidence around the factory or in any other areas of Osaka between 2004 and 2007.

No results showed statistically significant high SIRs, and there were no significant clusters based on the spatial scan statistics. Therefore, we cannot conclude from our analysis that there is an increased risk of biliary tract cancer incidence around the printing factory.

Only one study examining SIRs for men and women working in the printing industry is available.[23] Vlaanderen et al reported that, in four Nordic countries (Finland, Iceland, Norway, and Sweden), the SIRs of liver cancer (ICD 10 codes: C22.0 and C22.1) and intrahepatic biliary tract cancer (C22.1) of all printers and related workers were significantly higher than in the general population.[23] However, no one has yet examined cancer clustering in areas where printing factories are located.

The "Expert Panel on Biliary Tract Cancer at printing factories", organized by the Ministry of Health, Labour and Welfare, concluded that 16 cases of biliary tract cancer in workers at the printing factory were related to occupational exposure to high concentrations of dichloromethane and 1,2-dichloropropane.[24] A recent report from November 30, 2014, confirmed that seven workers who were engaged in ink removal operations at small printing factories in Miyagi,

Table 1. Properties of clusters in order of smallest *P*-values reported by SaTScan

Sex	Cluster	Distance from the factory (km)	Radius of the cluster (km)	Number of Cho-Aza[a] included in a cluster	Likelihood ratio	*P*-value	Observed cases	Expected cases	Standardized incidence ratio
Male	1 (The most likely cluster)	8.2	0.0	1	8.599	0.196	2	0.01	199.1
	2	18.3	1.3	9	6.538	0.816	7	1.20	5.8
	3	8.6	1.2	21	6.441	0.855	23	9.83	2.3
	4	17.6	0.7	7	6.404	0.867	13	3.98	3.3
	5	27.5	0.6	3	5.781	0.973	6	1.00	6.0
	6	11.6	1.2	26	5.352	0.996	27	13.43	2.0
Female	1 (The most likely cluster)	11.7	0.7	4	8.933	0.157	10	1.81	5.5
	2	15.3	0.5	2	7.013	0.633	4	0.27	14.6
	3	4.3	1.7	22	6.896	0.661	30	14.09	2.1
	4	11.2	0.5	16	5.978	0.928	6	0.96	6.3
	5	10.0	1.3	25	5.829	0.953	15	5.37	2.8
	6	18.5	0.9	10	5.327	0.984	6	1.09	5.5
	7	23.0	0.6	4	5.240	0.997	4	0.44	9.0
	8	26.0	1.7	14	5.169	0.997	13	4.59	2.8
Both sexes	1 (The most likely cluster)	4.7	1.2	12	8.978	0.217	32	13.66	2.4
	2	8.2	0.0	1	8.167	0.348	2	0.01	160.4
	3	6.4	0.7	5	5.987	0.952	17	6.43	2.7
	4	8.8	1.9	39	5.777	0.965	59	36.76	1.6
	5	11.2	0.9	37	5.608	0.978	17	6.66	2.6
	6	23.0	0.6	4	5.230	0.996	6	1.11	5.4
	7	3.3	0.8	12	5.155	0.996	19	8.23	2.3

[a]Cho-Aza is the small geographic area which we used in the analysis. It is one of the elements of the address system in Japan and is much smaller than a municipality or a prefecture.

Fukuoka, and Hokkaido, Japan, have developed biliary tract cancer from being exposed to highly concentrated 1,2-dichloropropane during their work.[25] Although the accurate causal relationship between the concentration of exposure and the incidence of biliary tract cancer is still unknown, high-level exposure to these substances in a small space might cause biliary tract cancer.

There are some limitations to our analysis. The population-based cancer registry data did not include data from the occupational database and could not link to these data either. Although we excluded subjects who worked in the printing factory from our analysis, other potential cases related to print workers who worked in other printing factories were not excluded. We were therefore not able to comprehensively account for environmental risks of neighborhood residents in our analysis to examine whether distance from the printing factory was associated with incidence of biliary tract cancer and whether there was clustering of biliary tract cancer incidence around this printing factory in Osaka. In addition, known risk factors of biliary tract cancer, such as infection with hepatitis B and C viruses and liver flukes,[26] could not be considered in our analysis because of lack of prevalence data on those factors in such a small area of Osaka, Japan.

In conclusion, our study confirmed that the risk of biliary tract cancer was not associated with distance from one specific printing factory in Osaka, Japan. We did not observe spatial clusters of biliary tract cancer incidence in Osaka prefecture during the study period 2004–2007. Although we could not determine whether any substances had diffused outside this factory, we need to examine the future long-term effects of potential environmental contamination on the incidence of biliary tract cancer in residents of areas neighboring the printing factory. Further investigations are also needed in other areas of Japan.

ONLINE ONLY MATERIALS

eTable 1. Age-specific, crude, and age-standardized incidence rates in Osaka, Japan in 2004–2007.
eFigure 1A. Location of Osaka prefecture in Japan.
eFigure 1B. Municipalities and Cho-Aza in Osaka prefecture.
eAppendix 1. Spatial scan statistics to identify clusters.
Abstract in Japanese.

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Conflicts of interest: None declared.

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Original Article

Trends in Lung Cancer Incidence Rates by Histological Type in 1975–2008: A Population-Based Study in Osaka, Japan

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ABSTRACT

Background: Monitoring trends in lung cancer incidence and mortality is important for the evaluation of cancer control activities. We investigated recent trends in age-standardized incidence rates by histological type of lung cancer in Osaka, Japan.

Methods: Cancer incidence data for 1975–2008 were obtained from the Osaka Cancer Registry. Lung cancer mortality data with population data in Osaka during 1975–2012 were obtained from vital statistics. We examined trends in age-standardized incidence and mortality rates for all histological types and age-standardized incidence rates by histological type and age group using a joinpoint regression model.

Results: The age-standardized incidence rate of lung cancer levelled off or slightly increased from 1975–2008, with an annual percentage change of 0.3% (95% confidence interval [CI], 0.1%–0.4%) for males and 1.1% (95% CI, 0.9%–1.3%) for females, and the mortality rate decreased by 0.9% (95% CI, 1.2%–0.7%) for males and 0.5% (95% CI, 0.8%–0.3%) for females. The incidence rates of squamous cell carcinoma (SQC) and small cell carcinoma (SMC) significantly decreased for both genders, whereas that of adenocarcinoma (ADC) significantly increased among almost all age groups in both genders.

Conclusions: The incidence rates of SQC and SMC decreased with the decline in smoking prevalence, which probably explains the change in trends in the incidence rates of lung cancer from the mid-1980s. However, the reason for the increase in ADC remains unclear. Therefore, trends in incidence rates of lung cancer should be carefully monitored, especially for ADC, and the associations between ADC and its possible risk factors should be studied.

Key words: cancer; lung cancer; incidence; histological type; cancer registries

INTRODUCTION

In Japan, incidence rates of lung cancer have levelled off for males and are increasing for females. Mortality rates of lung cancer show a decreasing trend for males and have levelled off for females.[1] It was previously reported that incidence rates of lung cancer in Osaka had levelled off for males but increased for females, and that mortality rates showed a slightly decreasing trend for males and females in an analysis using the joinpoint regression model.[2]

Smoking is a major risk factor for lung cancer. The population attributable fraction of active smoking to lung cancer mortality is about 70% for males and 20–40% for females.[3,4] However, trends for lung cancer incidence vary by histological type. Previously, it was reported that incidence rates of adenocarcinoma (ADC) increased and incidence rates of squamous cell carcinoma (SQC) and small cell carcinoma (SMC) decreased for both genders in Osaka, Japan.[5,6] Incidence rates of SQC and SMC increased among younger groups in their 40s and 50s and older groups aged more than 70 years in the 1990s, but decreased or levelled off among intermediate groups in their 60s. Incidence rates of ADC were reported to increase among most age groups.[7]

In the present study, we updated the trends in lung cancer incidence and mortality rates for all histological types and estimated incidence rates by histological type and age group in Osaka, Japan.

METHODS

Lung cancer incidence data for 1975–2008 were obtained from the Osaka Cancer Registry (OCR). Lung cancer

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mortality data in Osaka from 1975–2012 were obtained from vital statistics. Population data by sex and 5-year age group in Osaka were obtained from the National Census. This study was approved by the data usage committee of the OCR at the Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan) in August 2014 (approval ID: No. 14-0008).

When analyzing incidence rates by histological type, we followed the histological classification for lung tumors published by the World Health Organization.[8] Histological types were categorized as follows: SQC (International Classification of Diseases for Oncology Third Edition, Morphology [ICD-O-3M]: 8050–8078, and 8083–8084), ADC (ICD-O-3M: 8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, and 8576), SMC (ICD-O-3M: 8041–8045, and 8246), unspecified malignant neoplasm (ICD-O-3M: 8000–8005), and other specified malignant neoplasm. The data from the OCR included cases without specific histological diagnosis and stage. To include the missing data for histological type and stage in our analysis, we applied multiple imputation (MI).[9,10] For the imputation, we used a multinomial logistic regression model that included another incomplete variable and the complete variables: sex, age at diagnosis, period of diagnosis, and vital status. For the MI method, we used the *ice* command in Stata version 12 (STATA Corporation, College Station, TX, USA) and obtained 10 complete data sets.[11,12] When analyzing incidence rates by age group, age at diagnosis was classified into three categories: 35–64 years old, 65–74 years old, and over 75 years old, which were age-standardized within those age ranges.

First, we calculated annual age-standardized incidence and mortality rates (ASR) of lung cancer for all histological types and truncated age-standardized incidence rates by age group. We used the Japanese model population for 1985 to standardize age distribution. When analyzing by histological type, we used the 10 complete data sets obtained from the MI method. Second, we applied the joinpoint regression model[13,14] to identify the years when the statistically significant changes in incidence or mortality trends occurred using the Joinpoint Regression Program 4.1.0 (National Cancer Institute Surveillance Research Program Statistical Methodology and Applications Branch, Bethesda, MD, USA).[15] In the joinpoint analysis, we used the logarithmic ASR as the dependent variable and the year of diagnosis or death as the independent variable. We found the best joinpoints (years when trends changed) using the permutation test method. Annual percentage change (APC) of each line segment between joinpoints was estimated in the model, and the APC was tested to see whether it was significantly different from 0 ($P < 0.05$). We set three joinpoints as a maximum number in each analysis. We used Stata version 12 for all analyses except the joinpoint regression analysis.[11]

RESULTS

The characteristics of patients before and after multiple imputation are shown in Table 1. The proportion of patients with ADC increased while that with SQC and SMC decreased from the 1990s, and ADC has become a major histological type for both genders. The proportion of patients in the older age group (>75 years old) increased, while that of the younger age group (<65 years old) decreased.

Trends in lung cancer incidence and mortality rates for all histological types are shown in Figure 1 and Table 2. Incidence rates steeply increased by 3.5% (95% CI, 2.9%–4.1%) per year for males and 3.7% (95% CI, 2.6%–4.8%) per year for females until 1985–86. Trends in incidence rates then slightly increased, as APC was 0.3% (95% CI, 0.1%–0.4%) for males and 1.1% (95% CI, 0.9%–1.3%) for females. Mortality rates levelled off from 1988 and slightly decreased from 1997 for males (APC −0.9%; 95% CI, −1.2% to −0.7%). For females, mortality rates decreased from 1989 (APC −0.5%; 95% CI, −0.8% to −0.3%).

Figure 2 and Table 3 show trends in lung cancer incidence rates by histological type. The peak incidence of SQC was observed in 1996 for males and in 1986 for females. Incidence rates of SQC decreased for males (APC −1.9%; 95% CI, −2.4% to −1.5%) and females (APC −1.3%; 95% CI, −1.7% to −0.9%). ADC increased by 1.1% (95% CI, 0.8%–1.5%) for males and by 2.3% (95% CI, 2.1%–2.5%) for females. The rates of SMC decreased from 1992 for males (APC −0.9%; 95% CI, −1.3% to −0.4%) and from 1988 for females (APC −1.3%; 95% CI, −1.9% to −0.7%). The incidence rate of ADC overtook that of SQC for males in the 1990s.

We also analyzed truncated age-standardized incidence rates by histological type and age group (eFigure 1, eFigure 2, eFigure 3, eTable 1, eTable 2, and eTable 3). eFigure 1 and eTable 1 show trends in truncated (35–64 years, 65–74 years, and ≥75 years) age-standardized incidence rate of SQC by age group. For the age group 35–64 years, the rate continued to decrease in males (APC −1.0%; 95% CI, −1.3% to −0.8%), while it remained stable in females. For the age groups 65–74 years and ≥75 years, the rate significantly decreased for both genders. eFigure 2 and eTable 2 show trends in ADC. Among all age groups in males and females, except the age group 65–74 years in males, the rate significantly increased. The rate among the age group 65–74 years in males levelled off in 1997–2008. eFigure 3 and eTable 3 show trends in SMC by age group. Among the male age groups 35–64 years and 65–74 years and female age groups 65–74 years and ≥75 years, the rate decreased recently. However, the rate levelled off among the male age group ≥75 years and female age group 35–64 years.

Table 1. Characteristics of patients stratified by sex, diagnostic period, histological type, stage, and age group

	Year															
	1975–79		1980–84		1985–89		1990–94		1995–99		2000–04		2005–08		Total (1975–2008)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Males																
Histological type (before imputation[a])																
Squamous cell carcinoma	1038	18.6	1953	25.3	2664	25.8	2997	23.9	3936	25.1	4487	23.8	3853	22.0	20928	23.7
Adenocarcinoma	913	16.3	1702	22.0	2556	24.8	3023	24.1	4645	29.6	5909	31.3	5859	33.5	24607	27.9
Small cell carcinoma	321	5.7	754	9.8	1124	10.9	1395	11.1	1794	11.4	2134	11.3	1843	10.5	9365	10.6
Others	221	4.0	480	6.2	700	6.8	669	5.3	780	5.0	1028	5.4	1333	7.6	5211	5.9
Missing	3095	55.4	2841	36.8	3278	31.8	4440	35.5	4530	28.9	5325	28.2	4614	26.4	28123	31.9
Histological type (after imputation)																
Squamous cell carcinoma	2370	42.4	3200	41.4	3956	38.3	4740	37.9	5572	35.5	6423	34.0	5308	30.3	31568	35.8
Adenocarcinoma	1954	35.0	2628	34.0	3706	35.9	4555	36.4	6432	41.0	7986	42.3	7801	44.6	35062	39.7
Small cell carcinoma	772	13.8	1168	15.1	168	16.3	2177	17.4	2584	16.5	3072	16.3	2613	14.9	14069	15.9
Others	492	8.8	735	9.5	977	9.5	1052	8.4	1098	7.0	1403	7.4	1780	10.2	7536	8.5
Stage[b] (before imputation)																
Localised	657	11.8	867	11.2	1158	11.2	1340	10.7	2022	12.9	2694	14.3	2797	16.0	11535	13.1
Regional	1525	27.3	2078	26.9	2900	28.1	3377	27.0	4209	26.8	4694	24.9	4077	23.3	22860	25.9
Distant	1121	20.1	1949	25.2	2757	26.7	2997	23.9	3840	24.5	4929	26.1	5334	30.5	22927	26.0
Missing	2285	40.9	2836	36.7	3507	34.0	4810	38.4	5614	35.8	6566	34.8	5294	30.3	30912	35.0
Stage (after imputation)																
Localised	1084	19.4	1404	18.2	1756	17.0	2142	17.1	2943	18.8	3814	20.2	3497	20.0	16640	18.9
Regional	2492	44.6	3290	42.6	4351	42.2	5380	43.0	6521	41.6	7414	39.3	6048	34.6	35496	40.2
Distant	2012	36.0	3037	39.3	4214	40.8	5003	40.0	6220	39.7	7655	40.5	7957	45.5	36098	40.9
Age group, years																
15–34	42	0.8	45	0.6	34	0.3	43	0.3	43	0.3	57	0.3	32	0.2	296	0.3
35–64	2077	37.2	2561	33.1	3547	34.4	4105	32.8	4684	29.9	5129	27.2	4200	24.0	26303	29.8
65–74	2276	40.7	3040	39.3	3466	33.6	4141	33.1	5731	36.5	6853	36.3	6093	34.8	31600	35.8
≥75	1193	21.4	2084	27.0	3275	31.7	4235	33.8	5227	33.3	6844	36.2	7177	41.0	30035	34.0
Females																
Histological type (before imputation)																
Squamous cell carcinoma	170	8.1	285	9.7	472	11.6	504	9.9	677	10.4	759	9.4	641	8.5	3508	9.7
Adenocarcinoma	507	24.1	970	33.1	1443	35.5	1862	36.5	2850	43.8	3690	45.8	3722	49.5	15044	41.5
Small cell carcinoma	68	3.2	215	7.3	310	7.6	390	7.6	510	7.8	537	6.7	462	6.1	2492	6.9
Others	59	2.8	119	4.1	187	4.6	205	4.0	221	3.4	287	3.6	355	4.7	1433	4.0
Missing	1296	61.7	1341	45.8	1659	40.8	2145	42.0	2246	34.5	2777	34.5	2346	31.2	13810	38.1
Histological type (after imputation)																
Squamous cell carcinoma	454	21.6	584	20.0	801	19.7	936	18.3	1058	16.3	1241	15.4	981	13.0	6056	16.7
Adenocarcinoma	1269	60.4	1748	59.7	2420	59.5	3128	61.3	4295	66.0	5472	68.0	5275	70.1	23607	65.1
Small cell carcinoma	224	10.7	388	13.2	550	13.5	697	13.6	811	12.5	910	11.3	747	9.9	4326	11.9
Others	153	7.3	210	7.2	299	7.4	345	6.8	341	5.2	427	5.3	523	7.0	2299	6.3
Stage (before imputation)																
Localised	206	9.8	276	9.4	395	9.7	545	10.7	954	14.7	1549	19.2	1585	21.1	5510	15.2
Regional	540	25.7	662	22.6	951	23.4	1107	21.7	1504	23.1	1493	18.6	1338	17.8	7595	20.9
Distant	426	20.3	781	26.7	1099	27.0	1251	24.5	1527	23.5	2036	25.3	2067	27.5	9187	25.3
Missing	928	44.2	1211	41.3	1626	39.9	2203	43.2	2519	38.7	2972	36.9	2536	33.7	13995	38.6
Stage (after imputation)																
Localised	367	17.5	489	16.7	659	16.2	891	17.5	1354	20.8	2058	25.6	1914	25.4	7731	21.3
Regional	923	44.0	1169	39.9	1628	40.0	2013	39.4	2521	38.8	2716	33.7	2269	30.2	13239	36.5
Distant	810	38.6	1272	43.4	1784	43.8	2202	43.1	2629	40.4	3276	40.7	3343	44.4	15317	42.2
Age group, years																
15–34	32	1.5	24	0.8	25	0.6	27	0.5	27	0.4	33	0.4	25	0.3	193	0.5
35–64	798	38.0	960	32.8	1192	29.3	1460	28.6	1805	27.8	2128	26.4	1807	24.0	10150	28.0
65–74	786	37.4	1043	35.6	1343	33.0	1511	29.6	1830	28.1	2245	27.9	2166	28.8	10924	30.1
≥75	484	23.1	903	30.8	1511	37.1	2108	41.3	2842	43.7	3644	45.3	3528	46.9	15020	41.4

[a]The number and proportion by stage and histological type are calculated before and after multiple imputation.
[b]Stage at diagnosis is classified into three groups: localised (cancer is confined to the organ from which is originated, regional (cancer metastasizes into regional lymph nodes and/or invades adjacent organs), distant (cancer metastasizes to distant organs and/or lymph nodes).

DISCUSSION

Although trends in incidence and mortality rates steeply increased in parallel from 1975 to the 1980s, the incidence rate increased slightly and the mortality rate decreased slightly from 1980s onwards. The latest APC of incidence rates was higher for females than males (0.3% vs 1.1%). Histologically specific analysis showed a continuous increase in ADC and a decrease in SQC and SMC since around 1990.

Trends in the incidence and mortality rates for all histological types

Changes in incidence and mortality rates in the 1980s may be due to the decline in smoking prevalence because smoking habits are closely related to the incidence and mortality of lung cancer and other comorbidities.[3] The increasingly widespread use of computed tomography (CT) might in part have contributed to the slight increase in incidence and the slight decrease in mortality observed from the late 1980s.

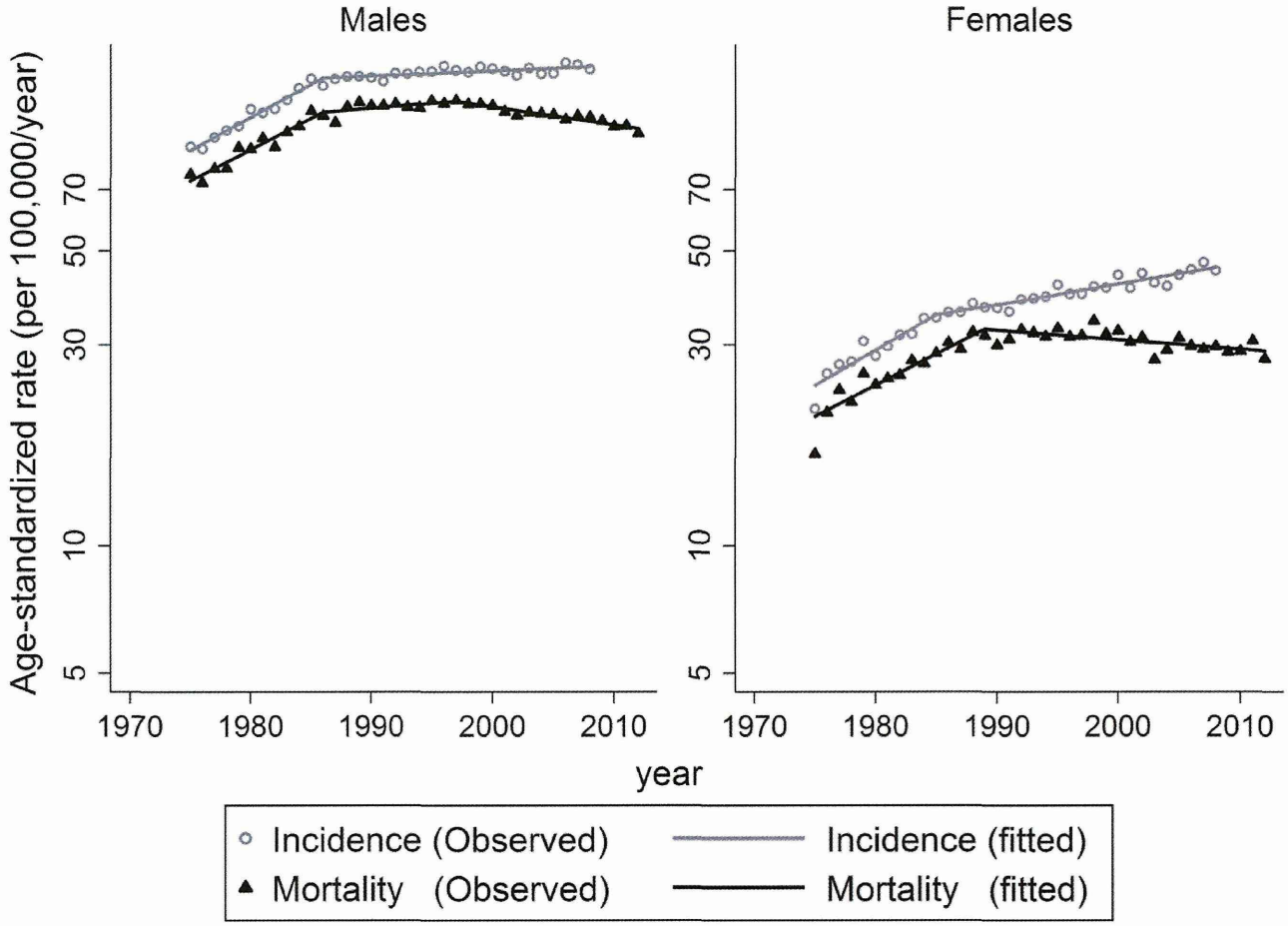

Figure 1. Trends in age-standardized incidence and mortality rates for lung cancer in Osaka, Japan from 1975 to 2008.

Table 2. Trends in age-standardized incidence and mortality rates of lung cancer with joinpoint analysis in Osaka, Japan

	Trend 1			Trend 2			Trend 3		
	Years	APC	(95% CI)	Years	APC	(95% CI)	Years	APC	(95% CI)
Incidence									
Males	1975–1986	3.5[a]	(2.9, 4.1)	1986–2008	0.3[a]	(0.1, 0.4)			
Females	1975–1985	3.7[a]	(2.6, 4.8)	1985–2008	1.1[a]	(0.9, 1.3)			
Mortality									
Males	1975–1988	3.0[a]	(2.5, 3.6)	1988–1997	0.2	(−0.5, 1.0)	1997–2012	−0.9[a]	(−1.2, −0.7)
Females	1975–1989	3.5[a]	(2.6, 4.4)	1989–2012	−0.5[a]	(−0.8, −0.3)			

APC, annual percentage change; CI, confidence interval.
[a]APC is statistically significantly different from zero ($P < 0.05$).

It has been reported that the detection rate of CT scanning is higher than that of x-ray or sputum cytology, and cases detected by CT are likely to be early stage and peripherally located ADC.[16,17] These cancers can be easily treated by surgery, which might have led to the decrease in mortality. However, low-dose CT screening, which was introduced in the 1990s in Japan, is experimentally conducted only in some specific areas, while CT scanning has been widely used in various clinical scenarios, such as chest pain, hemosputum, fever, faint abnormal shadow in chest x-ray, and screening for metastasis from other organ cancers. Therefore, it is difficult to evaluate the effects of CT scanning on the trends in lung cancer. The introduction and diffusion of tyrosine kinase inhibitors, such as gefitinib, which is an effective drug for advanced ADC with epidermal growth factor receptor (EGFR) mutations,[18] might also have partially contributed to the decrease in mortality.

To better understand these incidence and mortality trends, we also confirmed trends in the proportion of early stage cancer diagnosed as a localized cancer. In population-based