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The Geography of Cancer Mortality in Japan Focusing on Pancreatic Malignancies

Tsuyoshi TANABE*, Natsu YAMAGUCHI*, Mikiko KOBAYASHI-MIURA, Hiroki AMANO and Yasuyuki FUJITA

Department of Public Health, Environmental Medicine, Shimane University Faculty of Medicine, Izumo 693-8501, Japan

**These two authors contributed equally.*

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To identify pancreatic cancer's etiology and to better understand its pathogenesis, we assessed the-association between pancreatic and other cancers by determining the standardized mortality ratios（SMRs）. We calculated sex-specific and partial correlations（adjusting for lung cancer SMR）between pancreatic and other cancers in 47 Japanese prefectures. Comparing the results for the decades 1998-2007, 1988-1997, and 1978-1987 revealed that pancreatic cancer's SMR associates with those of lung, laryngeal, and bladder cancer in males, and stomach, colon, and rectal cancer in both sexes, and with ovarian cancer. The association with lung, laryngeal, and bladder cancer in males implicates tobacco smoking as a risk factor. The association with stomach cancer implies that *Helicobacter pylori* is a common risk factor. The association with colorectal cancer likely indicates that common factors such as obesity and high dietary fat may play etiological role. These results provide the clue to clarify the etiology of pancreatic cancer.

Key words: pancreatic cancer, SMR, geographical aggregation

INTRODUCTION

Unfortunately, pancreatic cancer tragically evades early detection, contributing to its poor prognosis [1]. In Japan, this tumor's age-adjusted mortality increased by approximately 9-fold in both sexes between 1950 and 1995 [2], representing the fifth and sixth leading cause of cancer deaths in 2006 in both genders, respectively [3]. Males' death risk from the disease exceeds that of females, and age-related mortality increases for both sexes after the forties [3, 4].

The well-established pancreatic cancer risk factor is smoking [5]. In Japan, the age-adjusted hazard ratio for smokers versus never-smokersis 1.58 in male, and the population-attributable fraction of disease-specific mortality for males is 26% [5]. Other pancreatic cancer risk factors include its familial history [6], diabetes [7, 8], chronic pancreatitis [9, 10, 11, 12], *Helicobacter pylori*（*H. pylori*）infection [11], genetic polymorphism of cancer related genes such as BRCA1 and BRCA2 [12], and hereditary pancreatitis [13]. Despite intensive efforts worldwide to uncover etiologies and to develop better diagnostics and therapeutics, pancreatic cancer is largely incurable.

Analyzing geographic associations to cancer rates is a valuable approach for uncovering risk factors and establishing new hypotheses on the pathogenesis and etiology of human diseases [14, 15, 16, 17], especially when the available knowledge is insufficient, as in the case of pancreatic cancer. Therefore, in the present study, we analyzed the association pancreatic cancer mortality with those of other cancers in each of Japan's 47 prefectures. We also analyzed the partial correlation for lung cancer to examine the influence of tobacco smoking on etiology of pancreatic cancer.

MATERIALS AND METHODS

Malignant neoplasms of the pancreas have been coded as 157 from 1965 to 1984 and 1985 to 1994, according to the International Classification of

Correspondence: Tsuyoshi Tanabe, MD, Ph. D,
Department of Public Health, Shimane University Faculty of Medicine
Enya-cho 89-1, Izumo, 693-8501, Japan
Tel:+81-853-20-2162
Fax:+81-853-20-2160
E-mail:ttanabe@med.shimane-u.ac.jp

Diseases (ICD-8th and ICD-9th Revision, respectively)[18]. The code was changed to C25 in 1995 (ICD 10th Revision)[19]. The number of deaths from 19 (oral cavity, pharynx, esophagus, stomach, colon, rectum, liver, gall bladder, larynx, lung, skin, prostate, bladder, breast, uterus, ovary, central nerve system, malignant lymphoma, and leukemia), 8 (esophagus, stomach, rectum, liver, lung, breast, uterus, and leukemia), and 7 (esophagus, stomach, liver, lung, breast, uterus, and leukemia) different malignant neoplasms by year (1978-1987, 1988-1997, and 1998-2007, respectively), sex and each prefecture and the total for Japan were obtained from the National Vital Statistics [20]. The data of 19, 8, and 7 cancers were available for each of three decades (1978-1987, 1988-1997, and 1998-2007, respectively).

SMR was calculated by dividing observed deaths by expected death and multiplying 100. An SMR of 100 indicates that the SMR in the group being studied is the same as the overall, or standard population. A ratio less than 100 indicates a lower than average death rate; over 100 is a higher than average one. The expected deaths are derived from national population, while the observed deaths reflect the data from studied population which is each prefecture's population in the present study.

In calculating the standardized mortality ratio (SMR) in 1998-2007, the sum of 5-times the population in 2000 and 2005 in each prefecture and the total for Japan obtained from the National Vital Statistics, were regarded as each prefecture's population and the standardized population, respectively. Similarly, in calculating the SMR in 1988-1997 and 1978-1987, the sum of 5-times population in 1990 and 1995, and in 1980 and 1985 were regarded, respectively, as each prefecture's population and the standardized population.

The SMRs of 19, 8, and 7 cancers by year and sex for each of three decades (1978-1987, 1988-1997, and 1998-2007, respectively) in 47 prefectures were calculated according to the national population to examine geographic aggregation. Two-sided 95% confidential intervals for SMR were evaluated by multiplying by the correlation-coefficient based on the Poisson distribution [21]. The association between pancreatic cancer SMRs and each of those of 19, 8, 7 other malignant neoplasms in 1978-1987, 1988-1997, and 1998-2007, respectively, was analyzed by determining correlation coefficients. Spearman's rank-correlation coefficient was evaluated because the normality of pancreatic cancer SMRs were not assured.

In populations from industrialized countries, the incidence of lung cancer can be used as marker of past tobacco consumption [22]. In order to adjust for the possible effect of tobacco smoking, we also calculated partial correlation coefficients for each cancer after adjusting for the correlation between pancreatic and lung cancer. The statistical analyses were computed using SPSS software, Version 19.

RESULTS

(1) *SMR*

The SMRs of pancreatic cancer by sex between 1998-2007, 1988-1997, and 1978-1987 in 47 prefectural and city governments are shown in Table 1 and Fig.1. In general, compared to the national population, the pancreatic cancer SMR was higher in both sexes in northern (Hokkaido, Aomori, Miyagi, and Akita) and facing Japan sea (Tottori and Shimane) and lower in western and southern prefectures (Okinawa, Kagoshima, Yamaguchi, Tokushima, and Kagawa).

The SMR changed greatly in some prefectures. In Shimane prefecture among males, SMRs were significantly higher during 1998-2007 (112.5) and 1988-1997 (113.3) than in 1978-1987 (94.2), and the rank rose to sixth and fourth, respectively, from thirty-third place. The SMRs for females in Shimane prefecture were significantly higher during 1998-2007 (107.7) than in 1978-1987 (92.9) and 1988-1997 (99.8). The rank rose to fifth place from thirty-fifth and twentieth place, respectively. For females in Fukui prefecture, SMRs were significantly higher during 1998-2007 (106.5) and 1988-1997 (107.2) than in 1978-1987 (92.1), and the rank rose to sixth and sixth place from thirty-ninth place, respectively. Conversely, in Fukushima prefecture, females SMRs decreased from 111.4 (1978-1987) to 106.8 (1988-1997) and 99.6 (1998-2007), and the rank dropped from fourth to seventh and to twenty first, respectively. Fukuoka prefecture fe-

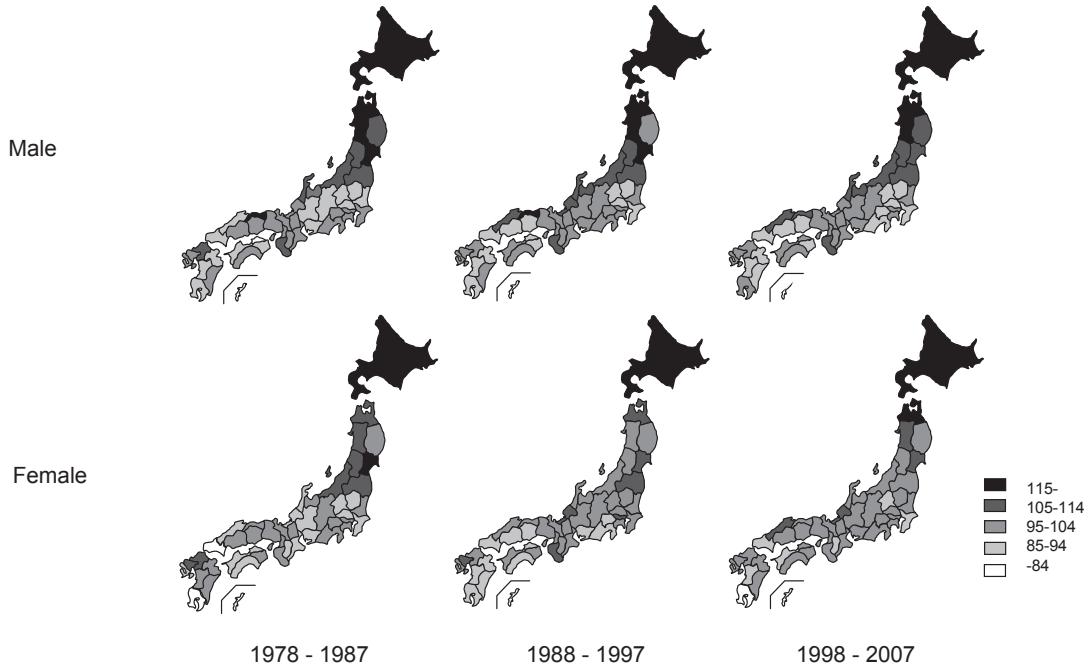

Fig. 1. SMR for pancreatic cancer in the 47 prefecture during three period every ten years from 1978 to 2007

Table 1. SMR and rank of pancreatic cancer in 47 prefectures in Japan during the period of every ten years from 1978 to 2007

Prefecture	Male						Female					
	1978–1987		1988–1997		1998–2007		1978–1987		1988–1997		1998–2007	
	SMR	rank	SMR	rank	SMR	rank	SMR	rank	SMR	rank	SMR	rank
Hokkaido	131.3	1	125.6	2	125.4	2	131.0	1	126.9	1	121.3	1
Aomori	130.7	2	131.0	1	126.2	1	113.2	3	113.6	2	116.1	2
Iwate	108.8	8	103.7	15	106.9	10	103.9	13	101.3	14	102.6	13
Miyagi	118.9	3	117.9	4	109.1	7	121.8	2	108.4	3	113.3	3
Akita	115.1	5	124.7	3	119.2	3	107.5	7	101.3	15	108.3	4
Yamagata	109.7	6	109.4	10	106.8	11	106.6	8	100.8	17	98.1	25
Fukushima	109.3	7	108.8	12	105.3	13	111.4	4	106.8	7	99.6	21
Ibaraki	92.5	37	98.9	22	98.5	24	98.5	22	103.6	11	101.5	16
Tochigi	91.6	39	93.1	37	90.7	44	92.9	36	97.4	26	97.2	31
Gunma	85.0	45	85.6	46	94.4	35	90.8	43	96.8	31	94.9	41
Saitama	91.2	40	93.3	36	91.8	43	92.4	38	96.9	29	99.8	20
Chiba	95.6	28	94.6	35	93.8	38	92.1	40	97.0	28	95.0	40
Tokyo	101.5	18	98.6	23	95.8	31	102.0	15	105.8	8	103.9	9
Kanagawa	96.8	23	95.1	33	97.8	26	101.9	17	99.8	19	98.4	23
Niigata	106.5	11	109.2	11	112.4	5	105.3	9	103.9	10	102.3	14
Toyama	104.7	13	110.0	9	106.6	12	98.6	21	99.0	22	98.0	26
Ishikawa	105.1	12	110.1	8	107.3	9	93.9	33	102.9	13	103.8	10
Fukui	101.9	16	105.3	13	100.1	18	92.1	39	107.2	6	106.5	6
Yamanashi	102.2	15	97.0	31	94.8	34	101.9	16	94.9	35	97.1	33
Nagano	94.4	32	95.9	32	98.4	25	99.9	18	98.8	24	102.7	12
Gifu	87.0	44	101.2	19	95.6	32	87.8	44	95.4	34	97.7	27
Shizuoka	95.3	30	95.0	34	94.0	36	98.4	23	93.6	38	95.2	38
Aichi	91.9	38	97.4	29	96.7	30	94.9	30	93.7	37	97.2	32
Mie	100.5	20	97.5	28	97.7	28	92.8	37	97.2	27	97.6	28
Shiga	101.9	17	100.6	21	103.1	15	104.4	11	104.3	9	101.8	15
Kyoto	100.3	21	103.9	14	103.0	16	96.8	28	103.0	12	104.1	8
Osaka	96.1	26	101.0	20	99.6	21	97.5	26	100.6	18	99.8	19
Hyogo	100.6	19	97.6	27	99.3	22	98.9	19	98.8	23	95.2	37
Nara	96.7	24	97.1	30	101.5	17	91.9	41	96.5	32	93.7	42
Wakayama	106.9	10	112.9	7	108.3	8	97.0	27	107.4	5	104.7	7
Tottori	116.5	4	116.3	5	109.8	6	104.5	10	96.8	30	103.5	11
Shimane	94.2	33	113.3	6	112.5	4	92.9	35	99.8	20	107.7	5
Okayama	95.4	29	91.3	43	93.7	39	104.0	12	93.4	40	96.1	36
Hiroshima	95.1	31	91.9	40	93.6	40	97.9	24	92.5	41	96.9	34
Yamaguchi	88.5	42	91.7	41	94.0	37	83.9	45	88.3	45	85.4	45
Tokushima	87.7	43	87.3	45	90.6	45	96.6	29	99.2	21	97.5	29
Kagawa	84.6	46	93.0	38	97.5	29	93.4	34	90.6	43	97.4	30
Ehime	93.9	35	98.0	25	99.3	23	94.3	32	95.8	33	93.2	43
Kochi	96.1	27	97.9	26	97.8	27	90.9	42	94.3	36	99.9	18
Fukuoka	107.4	9	102.3	16	99.8	19	110.5	5	101.0	16	98.1	24
Saga	104.2	14	101.5	18	104.7	14	108.6	6	107.9	4	100.6	17
Nagasaki	96.5	25	102.2	17	99.8	20	94.6	31	98.2	25	95.1	39
Kumamoto	93.4	36	92.3	39	93.4	41	98.8	20	93.5	39	90.7	44
Oita	94.0	34	89.0	44	93.3	42	102.5	14	90.1	44	98.8	22
Miyazaki	96.8	22	98.3	24	90.0	46	97.7	25	92.1	42	96.8	35
Kagoshima	89.0	41	91.4	42	95.2	33	81.5	46	86.5	46	84.5	46
Okinawa	73.2	47	63.4	47	63.9	47	64.5	47	62.9	47	64.2	47

males SMRs decreased from 110.5 (1978-1987) to 101.0 (1988-1997) and to 98.1 (1998-2007), with its rank dropping from fifth to sixteenth, and then to twenty-fourth.

(2) *Association study*

For lung cancer, a positive, significant correlation was apparent among males based on the 1998-2007 data, but there was no suggestion of a positive correlation for the datasets in both sexes (Table 2). For stomach cancer, we detected a significantly moderate correlation in all data for male. In contrast, there were only weak correlations in the 1998-2007 and 1988-1997 data for females, but not in those for 1978-1987. The adjustment for lung cancer slightly decreased the correlation among males, but that did not influence the correlation among females. The degree of decrease in males was slightly more remarkable in 1998-2007 than in 1978-1987 and 1988-1997.

For colon cancer, the data correlated moderately between both sexes during 1998-2007. The adjustment for lung cancer slightly decreased the correlation among males, but not females. For rectal cancers, a weak and moderate correlation was present in 1998-2007 among males and females, respectively, and a moderate correlation was observed between both sexes in 1988-1997. The adjustment for lung cancer slightly decreased the correlation among males, but not for females. The extent of the decrease was slightly more remarkable in 1988-1997 than for 1998-2007.

For laryngeal cancer, a moderate correlation was present only in males. Adjusting for lung cancer slightly decreased the correlation only among males. A moderate correlation in males and a weak correlation in females with respect to bladder cancer were apparent in 1998-2007. Adjusting for lung cancer slightly decreased the correlation among males only. For ovarian cancer, a positive correlation was present in the 1998-2007 data that was not diminished after adjusting for lung cancer. The analyses for the cancers in the oral cavity, pharynges, esophagus, liver, gall bladder, skin, breast, uterus, prostate, central nerve system, malignant lymphoma, and leukemia did not significantly correlate with pancreatic cancer.

DISCUSSION

One of the most striking findings in our present study was the high SMRs for pancreatic cancer be-

Table 2. Coefficients of pair-wise correlation between the mortality of pancreatic cancer and selected neoplasms, and coefficients of partial correlation between them after adjustments of lung cancer mortality

	Cancer	1998–2007				1988–1997				1978–1987			
		correlation	*p*–values	ajusted	*p*–values	correlation	*p*–values	ajusted	*p*–values	correlation	*p*–values	ajusted	*p*–values
Male	Oral cavity, Pharynx	0.113	0.451	0.064	0.673								
	Esophagus	0.331	0.023	0.370	0.011	0.216	0.145	0.211	0.158	0.208	0.160	0.215	0.152
	Stomach	0.433	0.002	0.380	0.009	0.447	0.002	0.424	0.003	0.412	0.004	0.397	0.006
	Colon	0.448	0.002	0.370	0.011								
	Rectum	0.325	0.026	0.317	0.032	0.442	0.002	0.427	0.003				
	Liver	0.264	0.073	−0.340	0.021	−0.271	0.065	−0.340	0.021	−0.155	0.298	−0.294	0.048
	Gall bladder	0.385	0.008	0.460	0.001								
	Larynx	0.402	0.005	0.340	0.021								
	Lung	0.401	0.005			0.240	0.104			0.289	0.049		
	Skin	0.174	0.243	0.151	0.315								
	Prostate	−0.420	0.777	0.106	0.485								
	Bladder	0.467	0.001	0.390	0.007								
	Central nerve system	−0.015	0.921	−0.130	0.389								
	Malignant lymphoma	−0.031	0.838	−0.234	0.118								
	Leukemia	−0.011	0.940	−0.171	0.255	0.166	0.265	0.080	0.595	0.083	0.579	−0.026	0.865
Female	Oral cavity, Pharynx	0.260	0.077	0.319	0.031								
	Esophagus	0.269	0.067	0.321	0.029	0.344	0.018	0.340	0.021	0.102	0.496	0.083	0.585
	Stomach	0.303	0.038	0.307	0.038	0.393	0.006	0.400	0.006	0.092	0.539	0.113	0.456
	Colon	0.522	<0.001	0.564	<0.001								
	Rectum	0.535	<0.001	0.534	<0.001	0.521	<0.001	0.521	<0.001				
	Liver	−0.202	0.174	−0.158	0.294	−0.253	0.086	−0.314	0.034	−0.088	0.555	−0.139	0.358
	Gall bladder	0.224	0.131	0.184	0.220								
	Larynx	0.053	0.724	0.124	0.410								
	Lung	−0.158	0.288			0.051	0.734			0.120	0.421		
	Skin	−0.339	0.200	−0.327	0.027								
	Breast	0.079	0.600	0.155	0.303	0.281	0.055	0.280	0.059	0.202	0.174	0.172	0.252
	Uterus	−0.334	0.022	−0.298	0.044	−0.353	0.015	−0.460	0.001	−0.208	0.161	−0.324	0.028
	Ovary	0.402	0.005	0.429	0.003								
	Bladder	0.324	0.026	0.334	0.023								
	Central nerve system	−0.016	0.914	−0.028	0.855								
	Malignant lymphoma	−0.057	0.704	0.008	0.959								
	Leukemia	−0.035	0.813	0.013	0.930	−0.081	0.588	−0.123	0.417	0.225	0.129	0.214	0.153

tween 1978 and 2007 in the northern prefectures of Hokkaido and Tohoku. Both in Shimane and Fukui prefectures, SMRs during 1998-2007 increased when compared to those in 1978-1987: this was observed in both sexes in Shimane, only in female in Fukui. Moreover, colorectal cancer SMRs correlated with those of pancreatic cancer for both sexes, while stomach, laryngeal, and bladder cancer SMRs correlated in males, as well as ovarian cancer in female. Less consistent associations were identified with lung cancer among males.

Several studies on the geographical distribution of pancreatic cancer SMRs in Japan showed that death from pancreatic cancer accumulated in the northern prefectures of Hokkaido and Tohoku, between 1979 and 1987 [23]. Other reports also reported that pancreatic cancer SMR was high in Hokkaido and Tohoku between 1968 and 2002 [24]. In addition to northern part, Niigata and Shimane prefectures along the Sea of Japan were reported to have high pancreatic cancer SMR between 1998 and 2002 [25]. Our previous study revealed that the pancreatic cancer SMR for males in Shimane prefecture has continued to be significantly high since 1989. In addition, the SMR for both sexes showed significant increases during 1997 to 2006. Thus, our present findings confirm the results of previous reports.

The well-established pancreatic cancer risk factor is smoking. The high smoking rate in northern part of Japan (Hokkaido, Aomori, Akita, and Miyagi) in both sexes has been reported [26], implying that the high mortality rate of pancreatic cancer in the area is partly due to smoking. However, the smoking rate in Shimane and Tottori is low. Some unidentified factors, different from those in northern part of Japan, might cause the high mortality rate of pancreatic cancer in Shimane and Tottori.

Several studies have revealed correlations between the incidence or mortality of each cancer type. These include surveys of 38 European countries, North America, and Oceania during 1993–1997 [14], a survey of incidence rates in 63 European cancer registries during 1988-1992 [17], an analysis of 1969-1978 incidence rates in eight Canadian provinces [16], and a study of 1969-1978 mortality rates within the 20 Italian regions [15]. These are considered below in relation to our present study.

Our association analysis presented here showed that lung and pancreatic cancer SMRs correlated positively among males, but not females, during 1998-2007. In contrast, the European and American studies described above showed a correlation between pancreatic cancer and lung cancer for both sexes [14, 15, 16]. The relatively low smoking rate in Japanese females compared with that of the United States and Europe [27] may provide the explanation. There is concern that the correlation between the pancreatic cancer SMR and that of lung cancer might be due to the invasion or metastatic spread of pancreatic cancer. Although this is applies to other tumors such as liver, they did not significantly correlate in the present study, which implies that invasion and metastasis fails to explain the correlation.

Laryngeal and bladder cancer SMRs correlated moderately with that of pancreatic cancer among males during 1998-2007, and the correlation diminished after adjusting for lung cancer SMR, thereby implicating smoking as a common risk factor.

In contrast to our present results, the data from Europe, the United States, and Oceania among males did not correlate with pancreatic cancer [14, 15, 16, 17]. A study of mortality associated with tobacco smoking in Japan revealed that lung, laryngeal, pancreatic, and bladder cancers are tobacco-related [28]. Our results suggest the possibility that the relation of smoking to laryngeal and bladder cancer may be stronger in Japan than in Europe and United States, or there may be associated factors specific for Japan. With respect to bladder cancer SMR among females, our results showed a weak correlation with pancreatic cancer, but not as strong as those in Canada and Italy female, which showed moderate to strong correlations [15, 16].

The association of stomach and pancreatic cancer among males was universally moderate in the present study, but weak among females during 1998-1997 and 1998-2007. Although European studies reported an association between pancreatic and stomach cancer among males, we could find no reports describing a significant association among females. Recent reports have suggested an association between infection with *H. pylori* and the development of pancreatic cancer [29]. These find-

ings suggest that *H. pyrori* may play a role in both stomach and pancreas cancer risks.

Our present results showed an association with pancreatic and colorectal cancer in both sexes. A correlation between pancreatic and colon cancer was described in European, Canadian, and Italian studies [14, 15, 16, 17]. An epidemiological study showed that obesity, high dietary fat, and heavy alcohol drinking are risk factors for colorectal cancer [30]. An analysis of pancreatic cancer patients in Japan suggested that the sharp increase in the consumption of animal fats in recent years might account for the recent increase in pancreatic cancer mortality [31]. Our results might reflect common etiologic factors such as obesity and dietary fat. We also demonstrated here an association between pancreatic and ovarian cancer SMRs. Adjusting for lung cancer SMRs did not reduce the association, suggesting that the smoking is not a common etiological factor.

In conclusion, our analysis shows that cancers associate with pancreatic cancer are those of the lung, laryngeal, and bladder in males, and stomach, colon, and rectal cancer in both sexes, and then ovarian cancer. Tobacco smoking is a plausible explanation, at least in part, for the association of pancreatic cancer with lung, laryngeal, and bladder cancer for males only. The association with stomach cancer suggests that *H. pylori* is a common risk factor, while the association of colorectal cancer in both sexes likely implies that obesity and high dietary fat play an etiological role. Our results provide the clue to clarify the etiology and pathogenesis of pancreatic cancer.

REFERENCES

1) Michaud DS (2004) Epidemiology of pancreatic cancer. *Minerva Chir* 59: 99-111.

2) Lin Y, Tamakoshi A, Wakai K, Kawamura T, Aoki R, Kojima M, Ohno Y (1998) Descriptive epidemiology of pancreatic cancer in Japan. *J Epidemiol* 8: 52-59.

3) The Editorial Board of Cancer Statistics in Japan. Cancer Statistics in Japan 2008. [Cited 5 Nov 2008] Available from URL: ganjoho.ncc.go.jp/public/statistics/backnumber/2008_jp.html (in Japanese).

4) Tanaka M (2007) Pancreatic Cancer Registry Report 2007. Suizo 22: e1-427 (in Japanese).

5) Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, Tamakoshi A, Tsugane S, Sobue T (2008) Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *J Epidemiol* 18 (6): 251-64. Epub 2008 Dec 9.

6) Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griffin C, Cameron JL, Yeo CJ, Kern S, Hruban RH (2004) Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 64: 2634-2638.

7) Luo J, Iwasaki M, Inoue M, Sasazuki S, Otani T, Ye W, Tsugane S; JPHC Study Group (2007) Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan--the JPHC study. *Cancer Causes Control* 18: 603-612.

8) Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, Kurosawa M and Ohno Y (2002) Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. *Int J Cancer* 99: 742-746.

9) Kitagawa M (2004) Pancreatic cancer and chronic pancreatitis. Kan-Tan-Sui 48: 591-597 (in Japanese).

10) Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg A and Domellöf L (1993) Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 328: 1433-1437.

11) Trikudanathan G, Philip A, Dasanu CA, Baker WL (2011) Association between Helicobacter pylori Infection and Pancreatic Cancer. A Cumulative Meta-Analysis. *J Pancreas* 12: 26-31.

12) Canada.Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA (2006) Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario,

J Natl Cancer Inst 98(23): 1694-706..

13) Whitcomb DC, Applebaum S and Martin SP (1999) Hereditary pancreatitis and pancreatic carcinoma. *Ann N Y Acad Sci* 880: 201-209.

14) Boffetta P, Castaing M, Brennan P (2006) A geographic correlation study of the incidence of pancreatic and other cancers in Whites. *Eur J Epidemiol* 21(1): 39-46.

15) Moore MA, Park CB, Tsuda H (1999) European registry comparisons provide evidence of shared risk factors for renal, colon and gallbladder cancer development. *Eur J Cancer Prev* 8: 137-146.

16) Howe GR, Sherman GJ, Malhotra A (1984) Correlations between cancer incidence rates from the Canadian national cancer incidence reporting system, 1969-78. *J Natl Cancer Inst* 72: 585-591.

17) Yanai H, Inaba Y, Takagi H, Yamamoto S. (1979) Multivariate analysis of cancer mortalities for selected sites in 24 countries. *Environ Health Perspect* 32: 83-101.

18) World Health Organization. (1977) Manual of international statistical classification of diseases, injuries, and causes of death. Based on the recommendations of the ninth revision conference, 1975, adopted by twenty-nine World Health Assembly. World Health Organization, Geneva.

19) World Health Organization (1992) International statistical classification of diseases and related health problems, 10th revision(ICD-10), volume 1. World Health Organization, Geneva.

20) Fukutomi K and Hashimoto S (2008) Health statistics - Epidemiology, 4th revision. Nanzando, Tokyo.

21) Lawson AB and Kulldorff M (1999) A review of cluster detection methods. In: Disease Mapping and Risk Assessment for Pablic Health. (Lawson AB, Biggeri A, Bohning D, Lesaffre E, Viel JF and Bertollini R, ed.) pp. 99-110, John Wiley & Sons, New York.

22) Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr (1992) Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. *Lancet* 339: 1268–1278.

23) Kato I, Kuroishi T and Tominaga S (1990) Descriptive epidemiology of subsites of cancers of the liver, biliary tract and pancreas in Japan. *Jpn J Clin Oncol* 20: 232-237.

24) Seino T, Nakadaira H, Endoh K and Yamamoto M (2008) Changes in pancreatic cancer mortality, period patterns, and birth cohort patterns in Japan: analysis of mortality data in the period 1968-2002. *Environ Health Prev Med* 13: 234-242.

25) Seino T, Nakadaira H, Endoh K and Yamamoto M (2006) Descriptive epidemiologic studies on geographical clusterings of pancreatic cancer mortality and incidence. *Jpn J Hyg* 61: 366-74(in Japanese).

26) The Editorial Board of Cancer Statistics in Japan. Cancer Statistics in Japan. [Cited 26March 2010] Available from URL: http://ganjoho.jp/public/statistics/pub/statistics06.html (in Japanese).

27) OECD Health Data 2007

28) Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, Tamakoshi A, Tsugane S, Sobue T (2008) Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *J Epidemiol* 18(6): 251-64.

29) Trikudanathan G, Philip A, Dasanu CA, Baker WL.JOP. (2011) Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. 5; 12(1): 26-31.

30) Wynder EL (1975) The epidemiology of large bowel cancer. *Cancer Res* 35 (11 Pt. 2): 3388-94.

31) Hirayama T (1989) Epidemiology of pancreatic cancer in Japan. *Jpn J Clin Oncol* 19(3): 208-15.