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Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC)

Manami Inoue,[1] Kazuo Tajima,[1] Toshiro Takezaki,[1] Nobuyuki Hamajima,[1] Kaoru Hirose,[1] Hidemi Ito[1] and Suketami Tominaga[2]

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Background To clarify lifestyle factors that affect the risk of pancreatic cancer among the Japanese population, a nested case-control study was conducted using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan.

Methods The study subjects included 200 incident cases of pancreatic cancer and 2000 age-class frequency-matched cancer-free outpatients attending the baseline questionnaire of HERPACC in the period 1988–1999. Associations between lifestyles and the risk of pancreatic cancer were evaluated using odds ratios estimated by the unconditional logistic regression model, adjusting for potential confounding factors.

Results A positive family history of pancreatic cancer and a past or present history of diabetes significantly increased the risk of pancreatic cancer. In contrast, regular physical exercise, a regular bowel habit, and frequent consumption of raw vegetables appeared to be protective. Current alcohol drinkers showed decreased risk, but the opposite was the case for former drinkers. Current smoking did not affect the risk of pancreatic cancer, while former smokers showed a tendency for decreased risk. Compared with light smokers, heavy smokers showed a modest tendency for increase in risk, especially those who starting smoking at a younger age, but there were no clear tendencies for duration and pack-years of smoking.

Conclusions From these results it appears that smoking habit, which has long been considered a sole important determinant, has only a modest role, if any, in pancreatic cancer in Japanese.

Keywords Pancreatic cancer, risk factor, Japanese, nested case-control study

Pancreatic cancer is relatively uncommon in the world, accounting for only 2% of all incident cancer cases in 2000.[1] In Japan, age-standardized incidence and mortality rates increased for a few decades before levelling-off after 1985, although the numbers of incident cases and deaths continue to show consistent absolute increase due to the ageing of the population.[2] In the latest vital statistics, this cancer ranked as the fifth leading cause of cancer death.[3]

Previous studies have highlighted the difficulties in conducting case-control studies of pancreatic neoplasia because the cancers are generally rapidly fatal so that it is not easy to collect lifestyle information directly from cases when they are alive. Furthermore, evidence based on cohort studies has been limited due to relatively low incidence. Nevertheless, possible risk factors for pancreatic cancer have been identified, such as smoking, alcohol, coffee, and low vegetable and fruit intake.[4–23] Host-related factors such as diabetes, familial pancreatic cancer, and hormonal aspects have also been suggested[24–26] but only

[1] Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya 464-8681, Japan.

[2] Aichi Cancer Center, Nagoya 464-8681, Japan.

Correspondence: Manami Inoue, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1–1 Kanokoden Chikusa-ku Nagoya 464-8681, Japan. E-mail: minoue@aichi-cc.jp

cigarette smoking was generally recognized as important, and other modifiable factors have yet to be unequivocally identified. The previous studies were mainly conducted in Western populations where the rates of this cancer are high compared with in Asians. In spite of male predominance, the male to female ratio, which is generally correlated with the relative risk (RR) of smoking habit, is less than 2, decreasing with age. This casts doubt on the smoking habit being a strong determinant. Epidemiological studies of pancreatic cancer targeted on the Japanese population[27–30] and other Orientals[20] have been relatively few. Because of the high fatality of this cancer and the rapid ageing of the Japanese population, in particular, there is an urgent need to clarify risk and protective factors.

The present study was therefore conducted to obtain further epidemiological evidence on the association between lifestyle factors and pancreatic cancer in a Japanese population by means of a nested case-control study with data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center, Japan (HERPACC).[31]

Subjects and Methods

The HERPACC was started in Nagoya, Japan in 1988, with information on lifestyle factors routinely collected from all first-visit outpatients, using a self-administered questionnaire checked by a trained interviewer. Each patient is asked about his or her lifestyle when healthy or before the current symptoms developed. The questionnaire includes items on demographic characteristics, medical history, family history, smoking and drinking habits, regular physical exercise, dietary habits, and menstrual and reproductive history.

The Aichi Cancer Center Hospital (ACCH) is a typical domestic hospital, located in the central part of Japan, and over 95% of outpatients reside in the Tokai area, which has a population of 15 million. The ACCH accepts new outpatients who visit of their own volition with or without doctor's referral, as with most general hospitals in Japan. Therefore, even though the ACCH is called a cancer hospital, only 19% of all new outpatients have cancer. Among these non-cancer outpatients, 45% present with no abnormal findings by clinical examination and 35% present with benign non-specific diseases.[32] Our earlier evaluation of discrepancies in lifestyle between these outpatients and the general population selected by electoral roll suggested that some differences do generally exist between males and females, across age groups, and between seasons in specific food items where supply was seasonal. However, these were small between outpatients and the general population after adjustment for gender, age, and season.[33] Thus, non-cancer outpatients at ACCH can be regarded as appropriate controls for epidemiological studies.

The data are loaded into an HERPACC database and routinely linked with the hospital cancer registry system for updating. This project has been approved by the ethical review board of the prefectural government. Details of the questionnaire and data collection procedures have been described elsewhere.[31]

The present study is based on data collected between January 1988 and December 1999. Among all first-visit outpatients during this period (n = 86 440), the questionnaire was given to 78 755 subjects (91.1%). The remaining 7685 (8.9%) were excluded as too young (<18 years), because an interviewer was absent, or because the consultation visit was by someone other than the patients themselves. Out of 78 755 outpatients, 77 803 (98.8%) provided adequate responses to the questionnaire. In the present study, 6% of the questionnaires were filled out by proxies although the study subjects were present in all these cases.

Among these subjects, 14 958 incident cases of cancer (19.2%) were identified as diagnosed by the end of the year 2000 by means of a hospital-based and population-based cancer registry system. In the present study, all cases of pancreatic cancer newly diagnosed from the commencement of the questionnaire study to the end of the year 2000 were deemed eligible as case subjects, a total of 200 (122 males and 78 females). Controls were selected by random sampling from all cancer-free individuals without a past history of cancer, with comparable gender and age strata (1 case versus 10 referents). Consequently, 200 cases and 2000 controls were selected and used as study subjects.

For the analysis of smoking habit, status was categorized as never, former, and current smoker, the last being further divided by the number of cigarettes per day (⩽19 and ⩾20), age started (⩾20, 18–19, ⩽17 years), duration (⩽19, 20–39, ⩾40 years), and pack-years of smoking (⩽19, 20–39, ⩾40). Former smokers were defined as people who had quit smoking for at least 1 year. These subjects were further divided by duration after quitting smoking (1–10, 11–20, ⩾21 years).

Plausible risk or protective factors for pancreatic cancer, other than the smoking habit, were selected from the questionnaire items based on the previous studies. According to the strength of the age-adjusted association with these selected items, variables on family history of pancreatic cancer, history of diabetes, regular physical exercise, bowel habit, raw vegetable intake, and alcohol drinking were further selected for the multivariate analysis.

Odds ratios (OR) were used to describe associations. Multivariate-adjusted OR with the corresponding 95% CI associated with selected lifestyles were estimated by unconditional logistic regression model. Accordingly, variables like age and year of interview (continuous), season of interview (spring, summer, autumn, winter), family history of pancreatic cancer (yes, no), history of diabetes (yes, no), regular physical exercise (⩾2 times/week, less), bowel habit (every day, less), raw vegetable intake (every day, less), and alcohol drinking (current, former, never) were included in the model when the risk of each variable was estimated, together with variables for the smoking habit when the risk of the latter was estimated. Stata version 7[34] was used to perform the statistical analysis.

Results

The mean age of cases was 60.5 years (range 32–85 years). The males were a little younger than female cases (mean age: 60.2 and 61.1 years, respectively) (Table 1).

Table 2 shows adjusted OR and their 95% CI of pancreatic cancer according to selected lifestyle factors other than smoking habit. A positive family history of pancreatic cancer significantly elevated the risk (OR = 2.09, 95% CI: 1.01–4.33), along with a past or present history of diabetes (OR = 1.79, 95% CI: 1.08–2.97), especially in males (OR = 2.07, 95% CI: 1.14–3.74). Frequent regular physical exercise (⩾2 times per week) decreased the

Table 1 Age and gender distribution of pancreatic cancer cases and referent subjects

	Total		Male		Female	
	Referents (n = 2000)	Cases (n = 200)	Referents (n = 1220)	Cases (n = 122)	Referents (n = 780)	Cases (n = 78)
Age (years)						
Mean (± SD)	60.4 (±10.6)	60.5 (±10.6)	60.1 (±9.9)	60.2 (±10.0)	60.8 (±11.6)	61.1 (±11.6)
Range (min.–max.)	30–89	32–85	30–84	32–82	30–89	32–85
Age group						
30–39	80	8	30	3	50	5
40–49	200	20	120	12	80	8
50–59	620	62	410	41	210	21
60–69	720	72	480	48	240	24
70+	380	38	180	18	200	20

Table 2 Adjusted odds ratios (OR) and their 95% CI of pancreatic cancer with reference to selected lifestyles factors[a]

	Total				Male				Female			
	Referents	Cases	OR	95% CI	Referents	Cases	OR	95% CI	Referents	Cases	OR	95% CI
Family history of pancreatic cancer												
No	97.4	95.0	1.00		97.2	95.9	1.00		97.8	93.6	1.00	
Yes	2.6	5.0	**2.09**	**(1.01–4.33)**	2.8	4.1	1.72	(0.63–4.72)	2.2	6.4	2.67	(0.90–7.98)
History of diabetes												
No	93.1	89.0	1.00		92.0	86.1	1.00		94.9	93.6	1.00	
Yes	6.9	11.0	**1.79**	**(1.08–2.97)**	8.0	13.9	**2.07**	**(1.14–3.74)**	5.1	6.4	1.29	(0.46–3.56)
Regular physical exercise												
Less	77.7	85.0	1.00		77.4	84.4	1.00		78.0	85.9	1.00	
2+ times/week	22.3	15.0	0.66	(0.43–1.01)	22.6	15.6	0.73	(0.42–1.27)	22.0	14.1	0.55	(0.27–1.10)
Bowel habit												
Less	21.5	29.4	1.00		15.0	23.3	1.00		31.7	39.0	1.00	
Every day	78.6	70.6	**0.70**	**(0.49–0.99)**	85.0	76.7	0.63	(0.39–1.01)	68.3	61.0	0.77	(0.46–1.29)
Raw vegetable												
Less	58.6	69.0	1.00		59.6	70.5	1.00		42.2	46.1	1.00	
Every day	41.4	31.0	**0.71**	**(0.51–0.99)**	40.4	29.5	0.65	(0.42–1.01)	57.8	53.9	0.78	(0.46–1.31)
Alcohol drinking												
Never	50.2	55.5	1.00		32.0	37.7	1.00		78.6	83.3	1.00	
Ever	49.8	44.5	0.80	(0.57–1.12)	68.0	62.3	0.85	(0.56–21.27)	21.4	16.7	0.71	(0.37–1.37)
former	4.8	18.5	**3.70**	**(2.28–6.00)**	6.5	25.4	**3.98**	**(2.29–6.93)**	2.1	7.7	**3.20**	**(1.11–9.22)**
current	45.1	26.0	0.50	(0.34–0.73)	61.5	36.9	0.54	(0.34–0.85)	19.4	9.0	0.43	(0.19–0.98)

[a] Model includes age, gender (gender-combined analysis only), family history of pancreatic cancer, past/present history of diabetes, regular physical exercise, bowel habits, raw vegetable intake, and alcohol drinking.

pancreatic cancer risk (OR = 0.66, 95% CI: 0.43–1.01), as did a regular bowel habit (OR = 0.70, 95% CI: 0.49–0.99) and raw vegetable consumption (OR = 0.71, 95% CI: 0.51–0.99). Other vegetable and fruit variables also showed tendencies to reduce the risk, but without statistical significance. Current alcohol drinkers showed a significantly decreased risk of pancreatic cancer (OR = 0.50, 95% CI: 0.34–0.73), this being apparent in both males and in females. On the other hand, former drinkers showed a significantly increased risk of pancreatic cancer (OR = 3.70, 95% CI: 2.28–6.00). Together with potential confounding factors such as age, year, and season of interview, the variables in Table 2 were included into the model for risk estimates on smoking habit.

Table 3 lists multivariate OR and 95% CI according to smoking habit. Current smoking did not affect the risk of pancreatic cancer, while former smokers showed a tendency for decreased risk (OR = 0.60, 95% CI: 0.35–1.00), especially those who had quit smoking after a short duration (1–10 years) (OR = 0.42, 95% CI: 0.20–0.91). However, the data indicated that heavy smokers who smoke ⩾20 cigarettes per day are at greater risk, compared with light smokers consuming less. It also appeared that a younger age at starting smoking might result in higher risk, but there were no clear tendencies for age started, duration, and pack-years of smoking. Additional analysis demonstrated no clear association for passive smoking.

Discussion

The main purpose of the present study was to determine lifestyle factors which affect the risk of pancreatic cancer, including a smoking habit, long considered as an important determinant, among a typical Japanese population. From our results, we conclude that a positive family history of pancreatic cancer and past or present history of diabetes significantly increased the risk of pancreatic cancer, whereas frequent regular physical exercise (⩾2 times per week), a regular bowel habit, and raw vegetable consumption are associated with decreased risk.

Smoking has demonstrated only a modest impact on pancreatic cancer risk, and a number of previous epidemiological

Table 3 Adjusted[a] odds ratios (OR) and their 95% CI for pancreatic cancer with reference to tobacco smoking

	Total				Male				Female			
Tobacco smoking	Referents (%)	Cases (%)	OR	95% CI	Referents (%)	Cases (%)	OR	95% CI	Referents (%)	Cases (%)	OR	95% CI
Never	47.3	47.5	1.00		21.7	23.8	1.00		87.5	84.6	1.00	
Ever	52.7	52.5	0.92	(0.62–1.37)	78.3	76.2	0.80	(0.50–1.28)	12.5	15.4	1.26	(0.62–2.56)
Former	23.0	16.0	0.60	(0.35–1.00)	35.3	25.4	0.56	(0.32–1.00)	3.7	1.3	0.29	(0.04–2.37)
quit for 1–10 years	8.5	5.5	**0.42**	**(0.20–0.91)**	12.9	9.0	**0.42**	**(0.19–0.94)**	1.5	0.0	—	
quit for 11–20 years	7.4	6.0	0.81	(0.39–1.65)	11.3	9.0	0.74	(0.34–1.61)	1.4	1.3	—	
quit for ⩾21 years	6.9	4.5	0.65	(0.30–1.43)	10.9	7.4	0.62	(0.27–1.41)	0.8	0.0	—	
Current	29.7	36.5	1.14	(0.75–1.74)	43.0	50.8	0.99	(0.60–1.63)	8.7	14.1	1.77	(0.83–3.78)
Amount												
⩽19 cigarettes/day	20.6	21.0	0.99	(0.62–1.57)	28.4	25.4	0.77	(0.44–1.35)	8.3	14.1	—	
⩾20 cigarettes/day	9.1	15.5	1.65	(0.95–2.89)	14.6	25.4	1.51	(0.83–2.72)	0.4	0.0		
Trend			*P* < 0.05				*P* < 0.05				*n.s.*	
Age started												
⩾20 years old	24.2	28.5	1.10	(0.71–1.70)	34.4	37.7	0.91	(0.54–1.52)	8.1	14.1	—	
18–19 years old	4.2	6.0	1.33	(0.63–2.79)	6.5	9.8	1.34	(0.62–2.92)	0.5	0.0	—	
⩽17 years old	1.3	2.0	1.61	(0.50–5.18)	2.1	3.3	1.54	(0.47–5.08)	0.1	0.0	—	
Duration												
⩽19 years	1.9	1.5	0.90	(0.25–3.22)	1.4	1.6	1.00	(0.19–5.36)	2.6	84.6	0.67	(0.82–5.45)
20–39 years	15.0	20.5	1.34	(0.82–2.19)	21.9	28.7	1.19	(0.67–2.12)	4.4	1.3	2.10	(0.79–5.61)
⩾40 years	12.5	14.5	0.99	(0.57–1.72)	19.5	20.5	0.82	(0.44–1.54)	1.7	7.7	2.47	(0.67–9.10)
Pack-years												
⩽19 pack-years	5.7	4.0	0.74	(0.33–1.64)	6.1	3.3	1.00	(0.54–1.86)	5.0	5.1	1.43	(0.47–4.37)
20–39 pack-years	10.6	13.5	1.22	(0.71–2.10)	15.6	18.0	1.15	(0.66–2.02)	2.8	6.4	2.40	(0.79–7.26)
⩾40 pack-years	13.4	19.0	1.30	(0.77–2.17)	21.4	29.5	0.57	(0.32–1.02)	0.9	2.6	1.56	(0.27–9.07)

[a] Adjusted for age, gender (gender-combined analysis only), family history of pancreatic cancer, past/present history of diabetes, regular physical exercise, bowel habits, raw vegetable intake, and alcohol drinking.

studies pointed to the same conclusion,[4–8,10–16,20,27,28] despite the fact that tobacco smoking is regarded as the most important contributing risk factor for many cancers.

Regarding possible bias, because the method employed for data collection was prospective with data linkage to hospital- and population-based cancer registries, independent of our study base, the possibility that the overall null result for smoking may have resulted from selection of a subset of cases with a lower smoking prevalence than all pancreatic cancer patients is low, and if any, it would be non-differential. Likewise, another possible bias, a higher prevalence of smoking among controls than the general population, is unlikely according to our previous validity study.[33] It is also the case that strength of effects of smoking on cancer may vary between populations, and even for lung cancer for instance, the smoking RR is low in Japanese as compared with Western populations. Thus, some ethnic difference may exist regarding susceptibility to effects of smoking.

In experimental studies, although available data are limited, evidence for possible pancreatic carcinogens in tobacco smoke has been provided by induction of tumours by NNK (4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone) and its major metabolite[35,36] through blood or reflux bile.[37] One study on patients with hereditary pancreatitis, demonstrating a dramatically earlier age of diagnosis of pancreatic cancer with the smoking habit, suggests that smoking–genetic interactions may be important.[38]

Regarding alcohol drinking, the great majority of previous epidemiological studies with a focus on this parameter demonstrated no association with pancreatic cancer,[7,8,13,16,18,20] and there is no clear biological mechanism, although alcohol drinking is an important determinant of chronic pancreatitis, a suspected risk factor for pancreatic cancer.[21,22] If the reason for quitting were because of symptoms of chronic disease, this might explain our finding of increased risk in ex-drinkers.

Previous studies demonstrated decreased risks with high vegetable and fruit intake,[17,20,23,29] consistent with our results, and vitamin C is considered to be a major contributor. Regular physical exercise also appears to decrease the risk of pancreatic cancer in our population. The previous reports revealed an inconsistent association,[15,19] and it appears that the risk modification may vary with the type of physical activity, i.e. leisure time and occupational. The influence of physical activity should be considered in relation to obesity and insulin resistance, since it is known to reduce glucose intolerance and high body mass index (BMI) is associated with an increase in risk of hyperinsulinaemia and diabetes. Here we did not observe a significantly increased risk with BMI (data not shown), but in our Japanese population, BMI is distributed in a lower range than in Western countries and this may have been a confounding influence. Studies focusing on familial pancreatic cancer and a history of diabetes, reporting a positive association with this tumour, have suggested an important role of abnormal glucose metabolism in the aetiology,[24–26,39–41] although it is still under discussion whether diabetes is a determinant or a consequence of this cancer.[42] Possible mechanisms are explained by obesity through diabetes[17,43] and hyperinsulinaemia,[39] but the studies also pointed to potential interactions between host-related and environmental factors such as smoking. Further investigations targeting this issue are

needed to determine the preventable fraction of this cancer, but since the effects of smoking regarding pancreatic cancer appear to be moderate, the major focus should perhaps be on gene–environment interactions.

A number of methodological issues relevant to the present nested case-control study need consideration. The prospective design of the present study precludes the possibility of recall bias, since the information on lifestyle exposure was collected before the diagnosis. Potential for selection bias is also unlikely, and follow-up of the outcome status was conducted by data linkage, using population- and hospital-based cancer registries. We cannot preclude the possibility of loss to follow-up when the study subjects were diagnosed outside the defined area, but the misclassification, if any, is probably non-differential and underestimates the results. Since our study was based on an outpatient population, generalizability of the results is a concern. However, evaluation of discrepancies in lifestyle between these outpatients and the general population in the same geographical area selected by electoral roll confirmed that differences after adjustment for gender, age, and season were small.[33] Lack of compliance with the questionnaire request was negligible, since the response rate was 98.8%. Because the study subjects were outpatients, it is nevertheless possible that information was dependent on some symptom or illness, as for example with ex-drinkers or ex-smokers, even though each outpatient was asked about lifestyle factors when healthy or before the current symptoms developed.

Allowing for these methodological issues, our study failed to detect any consistent association between the smoking habit and occurrence of pancreatic cancer, and other factors such as family history of pancreatic cancer, history of diabetes, and infrequent physical exercise appear to have more risk influence in Japan. Further studies are now needed to give clues to interactions between smoking and other environmental or host-related factors, including the genetic background.

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KEY MESSAGES

- Lifestyle factors that affect the risk of pancreatic cancer including a smoking habit, long considered as an important determinant, were investigated among a Japanese population by nested case-control study design.
- A positive family history of pancreatic cancer and past or present history of diabetes significantly increased the risk of pancreatic cancer, and frequent physical exercise, a regular bowel habit, and raw vegetable consumption were associated with decreased risk.
- Smoking has only a modest impact on pancreatic cancer risk in this population.

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