Establishment of risk model for pancreatic cancer in Chinese Han population

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Abstract

AIM: To investigate risk factors for pancreatic cancer and establish a risk model for Han population.

METHODS: This population-based case-control study was carried out from January 2002 to April 2004. One hundred and nineteen pancreatic cancer patients and 238 healthy people completed the questionnaire which was used for risk factor analysis. Logistic regression analysis was used to calculate odds ratio (ORs), 95% confidence intervals (Cls) and β value, which were further used to establish the risk model.

RESULTS: According to the study, people who have smoked more than 17 pack-years had a higher risk to develop pancreatic cancer compared to non-smokers or light smokers (not more than 17 pack-years) (OR 1.98; 95% CI 1.11-3.49, $P = 0.017$). More importantly, heavy smokers in men had increased risk for developing pancreatic cancer (OR 2.11; 95%CI 1.18-3.78, $P = 0.012$) than women. Heavy alcohol drinkers (>20 cup-years) had increased risk for pancreatic cancer (OR 3.68; 95%CI 1.60-8.44). Daily diet with high meat intake was also linked to pancreatic cancer. Moreover, 18.5% of the pancreatic cancer patients had diabetes mellitus compared to the control group of 5.8% ($P = 0.0003$). Typical symptoms of pancreatic cancer were anorexia, upper abdominal pain, bloating, jaundice and weight loss. Each risk factor was assigned a value to represent its importance associated with pancreatic cancer. Subsequently by adding all the points together, a risk scoring model was established with a value higher than 45 as being at risk to develop pancreatic cancer.

CONCLUSION: Smoking, drinking, high meat diet and diabetes are major risk factors for pancreatic cancer. A risk model for pancreatic cancer in Chinese Han population has been established with an 88.9% sensitivity and a 97.6% specificity.

INTRODUCTION

Pancreatic cancer is one of the most deadly cancers in the world. The mortality over morbidity ratio is 0.99:1. Only 10% patients have cancer cells confined in pancreas at the time of diagnosis, 40% have local invasion and 50% have distal metastasis. Although surgery, radiotherapy and chemotherapy have improved the life quality and survival rate in the cancer patients, only 10% patients show significant improvement. Most patients die from the cancer after 4 to 6 mo from diagnosis. Niederhuber *et al*[1] reported that one-year survival rate was less than 20%, decreasing to 7% for three-year and 3% for five-year. It is proposed that the best way to reduce the mortality is to improve early detection of this deadly cancer. In this paper we analyzed the possible risk factors and symptoms that correlated to pancreatic cancer based on a questionnaire survey among pancreatic patients and control subjects, and established a risk model for cancer estimation with weighted scores of risk factors and symptoms in an attempt to help early detection of pancreatic cancer in Chinese Han population.

MATERIALS AND METHODS

Subjects

A total of 119 cases of pancreatic cancer included in this study were diagnosed by Peking Union Medical College Hospital (PUMCH) between January 2002 and April

Table 1 Diagnostic standards for pancreatic cancer
A. Confirmed diagnosis by pathology
B. A valid confirmation requires at least 2 of the following listed items of imaging tests
(1) Ultrasound indicates there are low-density area in pancreas, as well as pancreatic duct dilation and common bile duct and gall bladder swelling
(2) CT indicates local enlargement and mass occupying lesion in pancreas
(3) ERCP indicates discontinuity of pancreatic duct, having mouse-tail ending, stiff and irregular duct wall, or any pull sign and double-duct sign
(4) MREP indicates there are stenosis and dilation in pancreatic duct and/or bile duct and space-occupying lesion in pancreas
(5) EUS indicates there is low-density, occupying lesion in pancreas
(6) IDUS
(7) Angiography
(8) PET
C. Palpable mass in surgery and at least an item of radiology evidence

ERCP: Endoscopic retrograde cholangiopancreatography
MREP: Magnetic resonance cholangiopancreatography
EUS: Endoscopic ultrasound sonography
IDUS: Intraductal ultrasound sonography
PET: Positron Emission Tomography

2004. The diagnosis was based on pathological, clinical and surgical evidence (Table 1). Among the 119 cases, 42 (35.3%) were confirmed by pathology; 17 (14.3%) by surgical findings; the rest (50.4%) by clinical findings. Those patients with a past history of chronic pancreatitis were diagnosed based on evidence of pancreatic calcification and pancreatic duct dilatation on imaging tests. All patients came from Beijing and its peripheral areas and were Han nationalities. The normal control group was randomly selected from normal general population in the same geographic area. The two groups were matched in gender and age and marriage status (Tables 2 and 3).

Methods
This is a case-controlled epidemiological study. We interviewed each subject in both groups based on a pre-determined questionnaire, which included questions about demographic data, smoking and drinking habits and family history of related diseases with pancreatic cancer. According to World Health Organization's definition of smoking, we defined the smokers as those who have smoked for 12 mo or more continuously or cumulatively in their lives. We measured the smoking history by the unit of pack-year which was defined as smoking of a package (20 pieces) of cigarette per day for one year. The number of pack-year = (the number of cigarette per day/20) × the number of years smoked. Because some persons used the pipe, we converted 50 g of pipe tobacco to 10 pieces of cigarettes. We defined the alcohol drinker as drinking at least twice a week and continuously for at least one year. Regarding the drinking volume, we adopted the unit of "drink", which was commonly used in North America. One drink contains 14 mL or 10.9 g of pure alcohol, which equals to 280 mL of beer (50 mL/L alcohol), 112 mL of wine (125 mL/L alcohol), 70 mL of rice wine (200 mL/L alcohol) or 35 mL of hard liquor (400 mL/L alcohol). In China, one bottle of beer is 640 mL, which is converted to 2.29 drinks. A glass of wine has 50 mL in volume, which

is 0.45 drink unit. One cup of hard liquor is 55 mL, which equals to 1.57 drink units. One cup of rice wine having 50 mL in volume is converted to 0.71 drink unit. We assumed the subject drank the same amount of alcohol per day per year. The total drinking volume is calculated by the following formula: Total volume (drink-years) = (Numbers of bottle of beer × 2.29 + Numbers of glass of wine × 0.45 + Numbers of cup of hard liquor × 1.57 + Numbers of cup of rice wine × 0.71) × (Numbers of drinking years). Because a large number of subjects in this study did not drink or only drank once in several weeks or months, we did not adopt the calculating method of gr (alcohol)/per day, which is often used to define heavy drinking.

According to the relative amount of meat and vegetable intake during most time of one's life, diet habit was divided into high meat consumption, high vegetable consumption and equal meat and vegetable consumption.

The high-risk scoring model was established on the basis of multivariate logistic regression analysis. The variables included risk factors and symptoms of pancreatic cancer. Possible risk factors and symptoms described in the questionnaire were compared between two groups with the t test or χ^2 test. The OR value of each factor was also calculated and those with statistical significance were listed. Combined with our clinical findings, significant and borderline risk factors and symptoms were selected as variables. With multivariate logistic regression analysis, we obtained regression coefficient β of each independent variable. Selecting the minimal β value as radix, and through division of every β value by the radix, the weighted numerical scores of each variable were derived. We made small adjustments to some scores based on the suggestions of some experts of epidemiology and gastroenterology and established the risk scoring model. The risk score of each patient could be calculated through simple addition of weighted score of each variable. The risk scores were compared between two groups by the t test. Receiver operating characteristic (ROC) curve was used to set a cutoff value for high cancer risk.

RESULTS
Analysis of risk factors for pancreatic cancer
The body mass index of pancreatic cancer patient was distinctively higher than that of control group. After correction by age and gender, the average weight index of patient group was 24.89 (17.99-36.73), while that of control group was 23.99 (14.53-32.74), with significant difference ($P = 0.033$) between these two groups. A clinical manifestation of pancreatic cancer patient was weight loss in a short term. Among the 109 patients who had weight index, the average weight loss was 6.70 (-5-31) kg during the one-year period before diagnosis. However, among the 197 control subjects who had weight index, their body weight increased by an average of 0.33 (-10.5-5) kg during the same period. The weight changes between the two groups had significant difference ($P < 0.0001$). Therefore, we used the weight index of the subjects one year before they were recruited into the study group.

Heavy smoking was shown as a risk factor for pancreatic cancer. There was no significant difference

Table 2 Inclusion and exclusion criteria for patients and controls

	Inclusion criteria	Exclusion criteria
Patients	(1) The patient voluntarily took part in this research; agreed to take necessary clinical examinations and answer epidemiological questionnaire survey; and give consent to the publication of research data. (2) Diagnosed by the pancreatic cancer team from PUMCH. (3) Clinical examination and epidemiological investigation were acceptable for the patient's condition. (4) Patient was diagnosed for pancreatic cancer between 2002 and 2004. (5) Patients did not undergo radiotherapy and anticancer therapy before surgery, and did not have other primary tumors. (6) Patients belonged to Han nationality.	(1) The patient did not agree upon the conditions to participate in the study or the patient information was not available at the inclusion time. (2) Not diagnosed by the pancreatic cancer team from PUMCH. (3) The patient's condition did not allow the clinical examination and epidemiological investigation. (4) The patient was not diagnosed for pancreatic cancer for the first time between 2002 and 2004. (5) Patients whose pancreatic tumor was a metastatic carcinoma or who had other tumors. (6) Patients were not from Han nationality.
Controls	(1) The person voluntarily took part in this research; agreeed to take necessary clinical examinations and answer epidemiological questionnaire survey; and give consent to the publication of research data. (2) The person did not have any kind of tumor. (3) The person matched with the patients for gender and age (±5 years). (4) Being the resident of Beijing or its peripheral area for at least 5 years. (5) Han nationality.	(1) The person did not agree upon the conditions to participate in the study or the person's information was not available at the inclusion time. (2) Person had any kind of malignant tumor. (3) Person suffered from severe coronary heart disease or stroke. (4) Person did not match with the patient group for gender and age (±5 years). (5) Not from Han nationality.

Table 3 Demographic characters of patients and controls

		Patients		Controls		χ^2	*P*
		n	(%)	*n*	(%)		
Age (yr)							
Male	≤50	16	(20.8)	36	(31.9)		
	50-59	17	(22.1)	27	(23.9)	3.6583	0.1606
	≥60	44	(57.1)	50	(44.3)		
Female	≤50	9	(21.4	28	(29.5)		
	50-59	8	(19.1)	26	(27.4)	3.1297	0.2091
	≥60	25	(59.5)	41	(43.2)		
Gender	Male	77	(64.7)	113	(54.3)		
	Female	42	(35.3)	95	(45.7)	3.3496	0.0672
Marriage status							
Married		115	(96.6)	183	(87.9)		
Divorced		0	(0)	7	(3.4)		
Widowed		4	(3.4)	16	(7.7)	8.093	0.082
Separated		0	(0)	1	(0.5)		
Spinsterhood		0	(0)	1	(0.5)		

between patient group (39.5%) and control group (35.92%) in terms of the percentage of smokers. After we divided each group into three subgroups (0, ≤17 package years and ≥17 package years) in terms of smoking history, we found significant differences between the patient group and control group. For those who smoked more than 17 package years (heavy smoker), the percentage of smokers accounted for 30.7% in patient group, which was 10% higher than that of control group. The risk of developing pancreatic cancer in the heavy smoker subgroup was 1.51 times that of the non-smokers (no statistic significance). When we combined the non-smoker and intermediate smoker subgroups (≤17 package years) together, it showed that the heavy smoker had increased risk of

pancreatic cancer (OR, 1.98; 95% CI, 1.11-3.49; $P = 0.017$). If divided by gender, there were more male heavy smokers in patient group (47.7%) than control group (30.3%). The risk of pancreatic cancer was increased for male heavy smokers (OR, 2.11; 95% CI, 1.18-3.87, $P = 0.012$). However, no conclusion for females was made due to the low percentage of smokers within the patient group and control group.

Heavy drinking was shown as a risk factor for pancreatic cancer. According to the median total drinking volume of control group, we divided the drinkers into three subgroups: non-drinking, low-drinking (≤20 drink-years) and heavy-drinking (>20 drink-years). The result indicated that the distribution frequencies of three subgroups in patient group were 74.0% (88/109), 5.9% (7/109) and 20.2% (24/109) respectively, while in control group were 84.5% (175/207), 8.2% (17/207), 7.3% (15/207) respectively. The distribution in patient group had significant difference from control group. After correction of age, gender and smoking factors, the OR value of low-drinking compared to the non-drinking was 1.003, while for the heavy-drinking subgroup, it increased to 3.681. Therefore, heavy-drinking had higher risk to develop pancreatic cancer.

Diet with high meat consumption was shown as a high risk for pancreatic cancer. In this study, we only explored the relationship between dietary habit and pancreatic cancer. The results showed that those who claimed meat as their major daily diet accounted for 31.0% of patient group, while the number dropped significantly to 7.6% in control group. For those who claimed vegetable was their major daily diet accounted for 39.7% (46/116) in patient group and 28.9% (57/197) in control group. The diet containing half meat and half vegetable was reported by 25.9% (30/116) of patient group and 57.9% (114/197)

Table 4 Benign digestive diseases in patients and controls

Diseases	Patients				Controls				P
	n	Yes	No	Not stated	n	Yes	No	Not stated	
Chronic pancreatitis	119	2.5	95.0	2.5	205	0.5	99.5	0	0.012
Acute pancreatitis	119	0	98.3	1.7	205	0	100	0	0.06
Cholelithiasis	119	10.01	89.1	0.8	205	4.9	95.1	0	0.08
Cholecystitis	118	9.3	87.3	3.4	205	0.5	99.5	0	<0.0001
Cholecystectomy	119	3.4	95.8	0.8	205	2.9	97.1	0	0.41

Table 5 Clinical symptoms of patients and controls

Symptom	Symptom duration (mo)[a]	Patients				Controls				P
		n	Yes	No	Not stated	n	Yes	No	Not stated	
Anorexia	2	118	45.8	54.2	0	203	0.5	99.5	0	<0.0001
Epigastric pain	3	119	60.5	38.7	0.8	181	2.2	97.8	0	<0.0001
Backache	2	119	32.8	66.4	0.8	205	2.0	98.1	0	<0.0001
Hypogastralgia	3	119	16.0	82.4	1.7	205	3.4	96.6	0	<0.0001
Abdominal pain	2	119	38.7	61.3	0	205	4.9	95.1	0	<0.0001
Jaundice	1	119	42.0	58.0	0	205	0.5	99.5	0	<0.0001
Skin itch	1	119	13.5	86.6	0	205	8.7	91.3	0	0.0032
Weight loss	3	119	76.5	22.7	0.8	205	2.4	97.6	0	<0.0001

of control group. Therefore, people who had meat as their major diet faced higher risk of developing pancreatic cancer.

Also we found that 18.5% patients with pancreatic cancer had a history of diabetic mellitus; however this ratio dropped to 5.8% in the control group. There was significant difference between patient group and control group in having chronic pancreatitis, cholelithiasis and cholecystitis (Table 4). Moreover, we asked each subject for any cancer family history among the primary and secondary generation relatives, but no significant differences were found between the two groups. In patient group, those who had a family history of cancer accounted for 26.9%, while in the control group was 31.3% ($P=0.4064$). For those who lost weight in patient group, 48.9% patients lost weight within 3 mo, 33.3% in 4-6 mo, 16.7% in 7-12 mo, and 1.1% in more than 1 year. In addition, 45. 6% of patients had weight lost less than 5 kg, 30.0% between 6 to 10 kg, and 24.4% more than 10 kg (Table 5).

Although most factors had significant difference between two groups, their OR value did not show significance except for smoking and drinking due to relatively small sample of this study.

Establishment of the high-risk scoring model of pancreatic cancer

With multivariable logistic regression and some adjustments, we established the high-risk scoring model (as shown in Table 6).

The score of pancreatic cancer group was 80.6 ± 30.0 (95% CI 74.9-86.3), and the score of normal control group was 7.4 ± 11.9(95% CI 6.0-8.7), ($P<0.001$, Mann-Whitney test). According to the scores of pancreatic group and normal control group, we protracted ROC curve and the area below the curve was 0.981. When selecting $\geqslant$ 45

as the differential cutoff between pancreatic cancer and normal control, the sensitivity and specificity of diagnosis were quite ideal, which were 88.9% and 97.6% respectively.

DISCUSSION

Because the two groups in our study were matched according to age and gender, there were no significant differences of the two factors. Based on previous studies on risk factors we included the two factors into high risk model. We have reported earlier that mortality of pancreatic cancer rises with age[2]. In a study involved 1619 cases of pancreatic cancer, 3.95% of the patients died before 40, but the mortality rate between 65 to 80 years was more than 5 times that of the average[2], which is consistent with other reports[3-6]. From 1991 to 2000, the epidemiological data of pancreatic cancer in China showed that the average male's mortality rate, revised mortality and standardized mortality grew 4.23%, 5.1% and 3.1% per year respectively, but the average growth rates for female were 7.7%, 8.6% and 6.74% respectively[2]. Although the gender disparity had been decreasing during this period, the increasing mortality rate in female has outpaced male. The age standardized mortality rate of male and female decreased from 1.97 in 1999 to 1.41 in 2000, which was consistent with report by Zheng et al[7].

Smoking is the only widely recognized risk factor for pancreatic cancer. Compared to non-smokers, the mortality rate of pancreatic cancer in smokers increased by 1.2-3.1 fold, and showed a dose-effect relationship. We found that the risk of pancreatic cancer occurrence increased in the heavy-smoking group (OR, 1.98; 95% CI, 1.11-3.49; $P=0.017$), which is consistent with previous literatures[4,8,9]. There was no consistent conclusion drawn for the risk of drinking associated with pancreatic cancer in literatures[4,10-12]. The OR value in the heavy-drinking

Table 6 Risk scoring model for pancreatic cancer		
Risk factor	**Criteria**	**Points**
Gender	Male	2
Age (yr)	>60	7
Alcohol drinking	>20 drink-yr	4
Smoking	>17 pack-yr	5
Diabetic mellitus history		17
High meat consumption		7
Family history of pancreatic cancer		15
Chronic pancreatitis		12
Cholelithiasis history		8
Cholecystitis history		1
Anorexia		25
Epigastric pain		25
Weight loss		37
Jaundice		30

subgroup was 3.70 (95% CI, 1.604-8.443) compared to non-drinking subgroup. Therefore, we considered the risk of drinking associated with pancreatic cancer mainly existed in the heavy-drinking patients. Immigration epidemiological research showed that the mortality rate of pancreatic cancer among Asian and African populations in their homeland was low. However, for Asians and Africans who lived in western countries and adopted western diet habits, the risk of having pancreatic cancer was similar to or even higher than the Caucasians[13]. From our study, the percentage of people who had high meat consumption in their daily diet was much higher in the patient group than in control group (*P* < 0.0001). Currently, 35% of pancreatic cancers were attributed to the dietary factor. It was reported earlier that the vegetable abundant diet could prevent 33%-50% of pancreatic cancer cases[14].

Whether diabetes is the etiologic factor or the early manifestation of pancreatic cancer is still controversial. When probing into the relationship between them, we cannot draw a conclusion because it is impossible to carry out a randomized prospective research. At the same time, it is difficult to obtain evidence from animal experiments because of lacking credible animal model for type II diabetes. Currently, most investigations have used case-control study and prospective cohort study in general population. In our case-control study, 18.5% of pancreatic cancer patients had diabetes history, while only 5.8% of the control group did. This finding is in accordance with other researches[15-18].

The relationship between chronic pancreatitis and pancreatic cancer is still under debate. Our study showed that 22.5% of pancreatic cancer patients had chronic pancreatitis while only 0.49% of control group did. Karlsen reported that the risk of pancreatic cancer increased 13 times from a follow-up investigation of 715 chronic pancreatitis patients for an average of 10 years during 1971 to 1995[19]. At the same time, the author noticed that the incidence of pancreatic cancer was much higher than non-pancreatic tumors among those patients.

A population based case-control study showed that performing cholecystectomy a year before the diagnosis of pancreatic cancer was related to the occurrence of pancreatic cancer. However, the risk gradually decreased along with the delay of the surgery, but still positively related[11]. Because pancreas and bile duct tumors are difficult to distinguish, some researchers believed that patients with concealed pancreatic tumor were likely to have cholecystectomy performed because of presumed cholelithiasis. However, we did not discover any relation between pancreatic cancer and cholecystectomy in our study. Therefore, it still awaits further clarification.

We established the high-risk scoring model on the basis of the results of case-control study and clinical experience. The risk factors in the high-risk model including smoking, weight loss and diabetes are basically the same as that of overseas studies. For instance, in the cancer risk index established by Harvard University[20], the risk factors for pancreatic cancer are smoking (moderate to high dose), family history of pancreatic cancer, diabetes, chronic pancreatitis and carbohydrate ingestion. In that index, they mainly do allotment of fraction according to the OR value of each risk factor. However, our model is to confirm the fraction of each factor according to the result of logistic multivariate regression, and it reveals the relative contribution of each risk factor to pancreatic cancer. Our risk model is to help clinical diagnosis, which is different from the cancer risk index of Harvard University whose purpose is cancer prevention. So we added the associated symptoms of pancreatic cancer to the risk model. Although the main symptoms of pancreatic cancer such as abdominal pain and jaundice usually appear late when the tumor is already in advanced stage, there are some non-specific symptoms such as anorexia and weight loss which are very obscure and easy to be overlooked by patients and doctors or mistakenly diagnosed as other diseases and functional abnormity[21,22]. So tackling the symptom clues might be helpful for screening and early diagnosis of pancreatic cancer. Our research showed that weight loss, epigastric pain and diabetes all had significant differences in the two groups, but weight loss in mo offers the best indication for diagnosis, so its score is the highest.

In conclusion, we have established a risk factor model for early screening of pancreatic cancer in Chinese Han population through case-control study. In future, we will apply this model in areas that have high incidence of pancreatic cancer in Han population to further improve our model.

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