

## RESEARCH ARTICLE

# Dietary Factors and Risk of Pancreatic Cancer: a Multi-Centre Case-Control Study in China

Shu-Zheng Liu<sup>1</sup>, Wan-Qing Chen<sup>2</sup>, Ning Wang<sup>3</sup>, Meng-Meng Yin<sup>1</sup>, Xi-Bin Sun<sup>1\*</sup>, Yu-Tong He<sup>4\*</sup>

## Abstract

**Background:** Pancreatic cancer is the sixth leading cause of cancer death with an increasing trend in China. Dietary intake is believed to play an important role in pancreatic cancer carcinogenesis. The aim of this paper was to evaluate associations between some dietary factors and risk of pancreatic cancer in a multi-centre case-control study conducted in China. **Materials and Methods:** Cases (n=323) were ascertained from four provincial cancer hospitals. Controls (n=323) were randomly selected from the family members of patients without pancreatic cancer in the same hospitals, 1:1 matched to cases by gender, age and study center. Data were collected with a questionnaire by personal interview. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using conditional logistic regression. **Results:** Tea intake (OR=0.49; 95% CI: 0.30-0.80) was associated with a half reduction in risk of pancreatic cancer. Reduced vegetable consumption (P trend: 0.04) was significant related to pancreatic cancer. Although no significant association was found for meat and fruit, ORs were all above or below the reference group. A protective effect was found for fruit (OR=1.73 for consumption of 1-2 times/week vs more than 3 times/week; 95% CI: 1.05-2.86). A high intake of meat was associated to a higher risk of pancreatic cancer (OR=0.59 for consumption of 1-2 times /week vs. more than 3 times /week; 95% CI: 0.35-0.97). **Conclusions:** The present study supports fruit consumption to reduce pancreatic cancer risk and indicates that high consumption of meat is related to an elevated risk. Direct inverse relations with tea and vegetable intake were also confirmed.

**Keywords:** Pancreatic cancer - risk factors - diet - tea - vegetables - China

*Asian Pac J Cancer Prev*, 15 (18), 7947-7950

## Introduction

Pancreatic cancer is the sixth leading cause of cancer death with increasing trend in china (Wang et al., 2003; Chen et al., 2013). The International Agency for Research on Cancer has estimated that 138,100 men and 127,900 women died from this malignancy worldwide in 2008 (Jemal et al., 2011). Pancreatic cancer often starts silently without symptoms at its early stage but progresses quite rapidly and has an extremely poor prognosis, with a 5-yr survival of 4% or less (Parkin, 2004; Lowenfels and Maisonneuve, 2006). A major challenge for the primary prevention of this disease is its largely unknown etiology. Although cigarette smoking has been established as a risk factor, it accounts for only about 22% of the total death in china (Wang et al., 2010). It is apparent that more risk factors need to be identified to enable the primary prevention of pancreatic cancer.

Diet intake is believed to play an important role in pancreatic cancer carcinogenesis. Red meat is possibly associated to an increased risk of pancreatic cancer,

whereas a protective effect of vegetable, fruit and tea is suggested (Zatonski et al., 1993; Polesel et al., 2010). In China, few studies have examined the association of dietary habits with pancreatic cancer risk, and all of them carried out in Shanghai (Ji et al., 1995a; Ji et al., 1995b; Ji et al., 1997; Wang et al., 2012; Wang et al., 2013).

The present study thereby sought to further investigate possible risk factors of dietary factors and habits for pancreatic cancer from a multi-center hospital-based case-control study conducted in China.

## Materials and Methods

### Study population

The study had a case-control design and was conducted in four hospitals (Henan Cancer Hospital, Beijing Cancer Hospital, Hebei Cancer Hospital and Cancer Institute and Hospital Chinese Academy of Medical Sciences.) between November 2011 and February 2013 in China. Cases were 323 newly diagnosed patients (181 men and 142 women; median age 58 years) of primary pancreatic

<sup>1</sup>Henan Cancer Research and Control Office, Henan Cancer Hospital, Zhengzhou, <sup>2</sup>National Office for Cancer Prevention and Control, Cancer Institute & Hospital, Chinese Academy of Medical Sciences, <sup>3</sup>Beijing Cancer Research and Control Office, Beijing Cancer Hospital, Beijing, <sup>4</sup>Hebei Cancer Research and Control Office, Hebei Cancer Hospital, Shijiazhuang, China \*For correspondence: xbsun21@sina.com, hytong69@yahoo.com

cancer, diagnosed no longer than 1 year before the interview. Histological confirmed neuro-endocrine tumors of the pancreas were excluded from the present study. 323 Controls (181 men and 142 women; median age 58 years) were randomly selected from the family members of the patients with no diagnosis of pancreatic cancer in the same hospital. They were 1:1 matched to cases by gender, age and study center. Less than 5% of cases and controls approached refused to participate.

#### Data collection

The study was approved by every hospital ethical committee. Before the interview, written, informed consent was obtained from all cases and controls. All participants were interviewed in person with a structured questionnaire during their hospital stay. The questionnaire included information on demographics, socioeconomics, personal medical history, selected lifestyle habits (e.g. tobacco smoking, alcohol drinking), food intake (kind and frequency), family history of cancer and, for women, menstrual and reproductive factors.

#### Statistical analysis

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for beverage and food intakes were calculated by means of logistic regression models conditioned on centre, sex, and age, and additional adjusted for possible confounders. The confounders initially adjusted in the regression models include ethnic group (Han and other), education (three levels), body mass index (two levels), cigarette smoking (no, yes), and Self-reported history of diabetes (no, yes). Ethnic group, education, body mass index was dropped from the final models because they did not substantively alter ORs (i.e., <10%).

Food groups were entered in the model based on frequency intake weekly. Considering frequency intake of food, the group (less than 1 times/week) was defined as the reference group for pickled foods, fried foods, bacon, fish, peanut, milk and bean. And the group (more than 3 times / week) was defined as the reference group for egg, meat, vegetable and fruits. The test for trend was based on the likelihood-ratio test between the models with and without linear terms for each variable of interest.

All analyses were performed using SPSS software (version 11.0), and a P-value of less than 0.05 was considered statistically significant.

## Results

Table 1 reports matching variables and baseline characteristics for cases and controls. The majority of study subjects were male (56.0%). The mean age ( $\pm$  standard deviation) of patients was 58.7 $\pm$ 11.2 years and 58.0 $\pm$ 11.2 years for controls. A direct association with pancreatic cancer emerged for tobacco smoking (OR=1.50; 95%CI=1.01-2.24) and self-reported history of diabetes (OR=2.69; 95%CI=1.51-4.77). Whereas the ethnic group, education and body mass index were not statistically different between cases and controls.

Table 2 shows the risks of pancreatic cancer in relation

to beverage. Alcohol and coffee were not related to pancreatic cancer. A nearly half risk of pancreatic cancer was reduced for tea drinking. An additional adjustment for cigarette smoking and diabetes did not materially alter the result above.

Table 3 shows the risk of pancreatic cancer according to consumption of foods. The association between pickled and fried foods and pancreatic cancer disappeared after further adjustment of cigarette smoking and diabetes. Reduced vegetable consumption was directly associated to pancreatic cancer risk (*P* trend: 0.04). No significant association was found for bacon, milk, meat, peanut, egg and fruit, but ORs were above or below the reference group for all levels of consumption of these foods. The protective effect was found for peanut (OR=0.56 for consumption of 1-2 times /week vs less than 1 times /week; 95%CI: 0.34-0.93) and fruit (OR=1.73 for consumption of 1-2 times /

**Table 1. Characteristics of 323 Cases and 323 Controls in a Hospital-based Case-control Study of Pancreatic Cancer in China**

	Case <sup>a</sup>		Control <sup>a</sup>		OR(95% CI) <sup>b</sup>
	N	(%)	N	(%)	
Centre Cancer Hospital					
Henan	110	(34.1)	110	(34.1)	
Beijing	105	(32.5)	105	(32.5)	
Hebei	73	(22.6)	73	(22.6)	
Cancer Institute & Hospital Chinese Academy of Medical Sciences					
Sex	35	(10.8)	35	(10.8)	
Male	181	(56.0)	181	(56.0)	
Female	142	(44.0)	142	(44.0)	
Age(years) <sup>c</sup>	58.7	(11.2)	58.0	(11.2)	
Ethnic group					
Han	312	(96.6)	314	(97.2)	1.00 (reference)
Other	9	(2.8)	9	(2.8)	1.22(0.51-2.95)
Education(years)					
<6	76	(25.0)	75	(23.7)	1.00 (reference)
6-12	111	(36.5)	118	(37.2)	0.91(0.57-1.46)
>12	117	(38.5)	124	(39.1)	0.87(0.50-1.51)
Body mass index (kg m <sup>-2</sup> )					
<25.0	243	(75.2)	260	(80.5)	1.00 (reference)
$\geq$ 25.0	80	(24.8)	63	(19.5)	1.43(0.95-2.14)
Cigarette smoking					
No	190	(58.8)	210	(65.0)	1.00 (reference)
Yes	133	(41.2)	113	(35.0)	1.50(1.01-2.24)
Self-reported history of diabetes					
No	174	(78.0)	255	(90.7)	1.00 (reference)
Yes	49	(22.0)	26	(9.3)	2.69(1.51-4.77)

<sup>a</sup>Sums may do not add up to total because of missing values; <sup>b</sup>ORs estimated from conditional logistic regression conditioned on centre, sex, and age; <sup>c</sup>Values given are means (s.d.).

**Table 2. Risk of Pancreatic Cancer in Relation to Beverage in a Hospital-Based, Case-Control Study of Pancreatic Cancer in China**

Beverage	Cases N(%)	Controls N(%)	OR(95% CI) <sup>a</sup>	OR(95% CI) <sup>b</sup>
Alcohol				
No	51 (15.8)	49 (15.2)	1.00 (reference)	1.00 (reference)
Yes	272 (84.2)	274 (84.8)	1.07 (0.65-1.76)	0.98 (0.50-1.95)
Tea				
No	240 (75.9)	208 (64.8)	1.00 (reference)	1.00 (reference)
Yes	76 (24.1)	113 (35.2)	0.53(0.36-0.79)	0.49(0.30-0.80)
Coffee				
No	308 (96.9)	297 (96.4)	1.00 (reference)	1.00 (reference)
Yes	10 (3.1)	11 (3.6)	0.90(0.37-2.22)	1.00(0.37-2.75)

<sup>a</sup>ORs estimated from conditional logistic regression conditioned on centre, sex, and age; <sup>b</sup>Additionally adjusted for cigarette smoking, Self-reported history of diabetes

**Table 3. Risk of Pancreatic Cancer in Relation to Food in a Hospital-Based, Case-Control Study of Pancreatic Cancer in China**

Food		frequency(times/week)			p trend <sup>a</sup>
		< 1	1-2	≥3	
Pickled foods	Cases/controls	204:185	58:91	53:45	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	0.56(0.37-0.84)	1.04(0.65-1.65)	0.03
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	0.73(0.43-1.23)	1.33(0.73-2.41)	0.68
Fried foods	Cases/controls	257:231	47:80	13:10	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	0.55(0.37-0.82)	1.13(0.47-2.72)	0.01
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	0.87(0.52-1.47)	1.17(0.4-3.42)	0.68
Bacon	Cases/controls	274:268	29:49	12:4	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	0.55(0.32-0.94)	2.39(0.75-7.58)	0.11
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	1.67(0.71-3.94)	3.21(0.64-16.11)	0.11
Fish	Cases/controls	135:134	123:148	61:40	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	0.83(0.58-1.17)	1.59(0.97-2.6)	0.69
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	0.62(0.4-0.97)	1.15(0.61-2.17)	0.09
Peanut	Cases/controls	121:106	113:133	85:83	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	0.74(0.51-1.08)	0.89(0.57-1.4)	0.16
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	0.56(0.34-0.93)	0.83(0.47-1.44)	0.05
Milk	Cases/controls	126:138	91:73	102:111	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	1.39(0.94-2.05)	1(0.67-1.5)	0.24
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	1.41(0.86-2.33)	1.03(0.6-1.75)	0.29
Bean	Cases/controls	135:147	132:118	52:57	
	OR1 (95% CI) <sup>b</sup>	1.00 (reference)	1.02(0.64-1.61)	1.23(0.78-1.94)	0.71
	OR2 (95% CI) <sup>c</sup>	1.00 (reference)	0.76(0.4-1.46)	1.07(0.57-2.01)	0.58
Egg	Cases/controls	38:34	93:85	188:203	
	OR1 (95% CI) <sup>b</sup>	1.26(0.76-2.08)	1.22(0.85-1.75)	1.00 (reference)	0.24
	OR2 (95% CI) <sup>c</sup>	1.53(0.8-2.91)	1.06(0.68-1.67)	1.00 (reference)	0.25
Meat	Cases/controls	64:52	111:125	143:145	
	OR1 (95% CI) <sup>b</sup>	1.26(0.78-2.03)	0.88(0.6-1.29)	1.00 (reference)	0.52
	OR2 (95% CI) <sup>c</sup>	0.91(0.49-1.72)	0.59(0.35-0.97)	1.00 (reference)	0.52
Vegetables	Cases/controls	4:2	25:11	290:309	
	OR1 (95% CI) <sup>b</sup>	2(0.37-10.92)	2.4(1.15-5.02)	1.00 (reference)	0.02
	OR2 (95% CI) <sup>c</sup>	1.80(0.33-9.90)	2.29(1.09-4.82)	1.00 (reference)	0.04
Fruits	Cases/controls	29:54	115:78	175:190	
	OR1 (95% CI) <sup>b</sup>	0.6(0.35-1.02)	1.73(1.16-2.58)	1.00 (reference)	0.55
	OR2 (95% CI) <sup>c</sup>	1.36(0.63-2.93)	1.73(1.05-2.86)	1.00 (reference)	0.11

<sup>a</sup>Linear trend across frequency of food intake; <sup>b</sup>OR estimated from conditional logistic regression conditioned on centre, sex, and age; <sup>c</sup>Additionally adjusted for cigarette smoking, Self-reported history of diabetes

week vs more than 3 times /week; 95%CI: 1.05-2.86). A high intake of meat was associated to a higher risk of pancreatic cancer (OR=0.59 for consumption of 1-2 times /week vs more than 3 times /week; 95%CI: 0.35-0.97).

## Discussion

The present study confirms the inverse association of tea and vegetable with pancreatic cancer. Moreover, it adds evidence to the risk of meat and the protected effect of fruit with pancreatic cancer.

Epidemiological data on the association between tea and pancreatic cancer are controversial. Lin et al has reported that green tea consumption does not decrease the risk for pancreatic cancer in Japanese adults (Lin et al., 2008). However, these findings are in sharp contrast to previous studies that support a pancreatic protective effect of tea. Several studies have shown that increased tea consumption is associated with a corresponding decline in the risk for pancreatic cancer (Whittemore et al., 1983; Zatonski et al., 1993; Shibata et al., 1994). One explanation for the contrary results is the possible impact and role of confounding factors such as geography and

race (Lin et al., 2008). A recent population-based case-control study in urban Shanghai has drawn the similar result with our study (Wang et al., 2012).

The significant inverse correlation between vegetables and the risk of pancreatic cancer is in agreement with a number of previous investigations. A multi-centre population-based case-control study in the United States discerned a statistically inverse relationship between cruciferous vegetables and the risk of pancreatic cancer in both males (OR=0.5,  $p=0.04$ ) and females (OR=0.4,  $p=0.002$ ) (Silverman, Swanson et al., 1998). In a case-control study in Canada, a reduced risk of pancreatic cancer was related to vegetables and vegetable products (OR=0.47; 95%CI: 0.21-1.06;  $p$ -trend=0.024) (Ghadirian and Nkondjock, 2010). The raw vegetable consumption was associated with decreased pancreatic cancer risk (OR=0.71, 95%CI: 0.51-0.99) in a nested, case-control study in Japan (Inoue et al., 2003).

A recent meta-analysis (Bae et al., 2009) reported a moderate inverse association for citrus fruits with current evidence suggesting that folate and folate-containing foods may exert a protective effect against pancreatic cancer (Larsson et al., 2006; Aune et al., 2009). And although

several studies observed no statistically significant association between fruits and pancreatic cancer risk, they all had risk estimates below unity (Olsen et al., 1989; Zheng et al., 1993; Shibata et al., 1994; Coughlin et al., 2000; Stolzenberg-Solomon et al., 2002). Similarly, in our investigation, the inverse association with fruits consumption was of borderline significance.

Several studies investigated the relation between meat intake and pancreatic cancer, suggesting a positive association (Stolzenberg-Solomon et al., 2007; Heinen et al., 2009; Polesel et al., 2010). And the relation was more evident for red meat. In our study, only borderline risk of pancreatic cancer to high intakes of meat was shown.

When commenting on our results, some limitations must be kept in mind. As in other case-control studies, the possibility of recall bias and selection problems cannot be ruled out completely. However, awareness of any hypothesis on dietary habits in pancreatic cancer was limited in the study population at the time of the study. And cases and controls were enrolled from the same hospitals with a multi-centre design.

In conclusion, our data suggest that fruits reduce pancreatic cancer risk and that high consumption of meat is related to an elevated risk. Findings from the present study confirm a direct inverse relation with tea and vegetable intake.

## Acknowledgements

This work is Supported by Cancer Institute and Hospital, Chinese Academy of Medical Sciences research funding (NO. 2010YF46). The authors declare no conflict of interest.

## References

Aune D, De S, Ronco A, et al (2009). Legume intake and the risk of cancer: a multisite case-control study in Uruguay. *Cancer Causes Control*, **20**, 1605-15.

Bae J, Lee E, Guyatt G (2009). Citrus fruit intake and pancreatic cancer risk: a quantitative systematic review. *Pancreas*, **38**, 168-74.

Chen W, Liang D, Zhang S, et al (2013). Pancreatic cancer incidence and mortality patterns in China, 2009. *Asian Pac J Cancer Prev*, **14**, 7321-4.

Coughlin S, Calle E, Patel A, et al (2000). Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control*, **11**, 915-23.

Ghadirian P, Nkondjock A (2010). Consumption of food groups and the risk of pancreatic cancer: a case-control study. *J Gastrointest Cancer*, **41**, 121-9.

Heinen M, Verhage B, Goldbohm R, et al (2009). Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. *Int J Cancer*, **125**, 1118-26.

Inoue M, Tajima K, Takezaki T, et al (2003). Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Int J Epidemiol*, **32**, 257-62.

Jemal A, Bray F, Center M, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Ji B, Chow W, Dai Q, et al (1995a). Cigarette smoking and alcohol consumption and the risk of pancreatic cancer:

a case-control study in Shanghai, China. *Cancer Causes Control*, **6**, 369-76.

Ji B, Chow W, Gridley G, et al (1995b). Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai China. *Cancer Epidemiol Biomarkers Prev*, **4**, 885-93.

Ji B, Chow W, Hsing A, et al (1997). Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer*, **70**, 255-8.

Larsson S, Hakansson N, Giovannucci E, et al (2006). Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. *J Natl Cancer Inst*, **98**, 407-13.

Lin Y, Kikuchi S, Tamakoshi A, et al (2008). Green tea consumption and the risk of pancreatic cancer in Japanese adults. *Pancreas*, **37**, 25-30.

Lowenfels A, Maisonneuve P (2006). Epidemiology and risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol*, **20**, 197-209.

Olsen G, Mandel J, Gibson R, et al (1989). A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health*, **79**, 1016-9.

Parkin D (2004). International variation. *Oncogene*, **23**, 6329-40.

Polesel J, Talamini R, Negri E, et al (2010). Dietary habits and risk of pancreatic cancer: an Italian case-control study. *Cancer Causes Control*, **21**, 493-500.

Shibata A, Mack T, Paganini-Hill A, et al (1994). A prospective study of pancreatic cancer in the elderly. *Int J Cancer*, **58**, 46-9.

Silverman D, Swanson C, Gridley G, et al (1998). Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst*, **90**, 1710-9.

Stolzenberg-Solomon R, Cross A, Silverman D, et al (2007). Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort. *Cancer Epidemiol Biomarkers Prev*, **16**, 2664-75.

Stolzenberg-Solomon R, Pietinen P, Taylor P, et al (2002). Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*, **155**, 783-92.

Wang J, Zhang W, Sun L, et al (2013). Dietary energy density is positively associated with risk of pancreatic cancer in urban Shanghai Chinese. *J Nutr*, **143**, 1626-9.

Wang J, Zhang W, Sun L, et al (2012). Green tea drinking and risk of pancreatic cancer: a large-scale, population-based case-control study in urban Shanghai. *Cancer Epidemiol*, **36**, 354-8.

Wang J, Jiang Y, Wei W, et al (2010). Estimation of cancer incidence and mortality attributable to smoking in China. *Cancer Causes Control*, **21**, 959-65.

Wang L, Yang G, Lu X, et al (2003). Pancreatic cancer mortality in China (1991-2000). *World J Gastroenterol*, **9**, 1819-23.

Whittemore A, Paffenbarger R, Anderson K, et al (1983). Early precursors of pancreatic cancer in college men. *J Chronic Dis*, **36**, 251-6.

Zatonski W, Boyle P, Przewozniak K, et al (1993). Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. *Int J Cancer*, **53**, 601-7.

Zheng W, McLaughlin J, Gridley G, et al (1993). A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*, **4**, 477-82.