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ORIGINAL ARTICLE

Dietary food groups intake and cooking methods associations with pancreatic cancer: A case–control study

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Abstract
Background The role of dietary habits in the etiology of pancreatic cancer (PC) has not yet been well elucidated.
Aim The aim of the present study was to examine the association of the frequency of different food groups' intake and their cooking methods with PC risk based on a well-designed case–control study.
Methods A case–control study including 307 PC patients and 322 controls referred to four tertiary endosonography centers was conducted from January 2011 to January 2014 to compare the frequency intake of different food items and their cooking methods between cases and controls.
Results After adjustment for gender, age, body mass index, years of education, diabetes and alcohol history, smoking status, and opium use, a significant direct relationship was observed between PC risk and intake frequency (time/week) of bread (OR=1.50; 95 % CI 1.05–2.13; *p*-value 0.024), rice (OR=2.10; 95 % CI 1.15–3.82; *p for trend* 0.034), and red meat (OR=2.25; 95 % CI 1.22–4.14; *p for trend* 0.033) (time/day), when comparing the highest category of intake frequency with the lowest, while increasing frequency of fish consumption was associated with a lower risk of PC (OR= 0.93; 95 % CI0.59–1.47; *p for trend* 0.009). Increasing consumption of barbecuing red meat and deep fried vegetables was associated with 67 % and 70 % increased risk of PC (*p*-value 0.025 and 0.006, respectively).
Conclusion Our results indicate that increased frequency of intake of bread, rice, and red meat (especially barbecued) and deep fried vegetables can aggregate PC risk, while increased frequency of fish consumption can protect against PC. However, more studies are still needed.

Keywords Case–control study · Cooking methods · Dietary factors · Pancreatic neoplasms

Introduction

Pancreatic cancer (PC) has identified as one of the most lethal malignancies worldwide with significant growing trend in its incidence in recent years [1, 2]. PC's overall 5-year relative survival rate has shown the least improvement in comparison to other cancers in recent years [3–6].

Through the lack of the PC's well-established risk factors and its major causes, primary prevention is the most possible approach to reduce the incidence of this malignancy. Therefore, finding main and particularly alterable risk factors and understanding the etiology of this fatal cancer is very important [4, 7].

Based on previous studies, cigarette smoking [1, 5, 8, 9], adiposity and obesity [1, 10], high body mass index (BMI) [5, 8, 9], increasing HbA1c levels [11], diabetes mellitus [1, 5, 8, 12], genetic factors and a family history of cancer (especially PC) [8, 9, 12, 13], alcohol abuse [1, 5], advancing age [5], physical activity [14], non-O blood group [1], social conditions in the presence of available effective preventions and treatments [15], and chronic pancreatitis [5, 8] are risk factors for PC.

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The association between diet and PC can be related to its well-known linkage with diabetes mellitus, insulin resistance, obesity, high BMI, and adiposity. However, the role of dietary habits, as one of the most modifiable environmental factor, in the etiology of PC has not yet been well elucidated [4, 14].

The aim of the present study was to examine the association of the frequency of different food item intake and their cooking methods with PC risk based on a well-designed case–control study.

Methods

Study population

The study protocol was approved by the Institutional Review Board of Digestive Disease Research Institute, Tehran University of Medical Sciences (IRB number IRB00001641, Federalwide Assurance number FWA00015916).

Study participants (322 controls and 307 cases) were recruited from patients who were referred for endoscopic ultrasound (EUS) to three tertiary referral hospitals (Shariati, Firoozgar, and Atieh Hospitals) or a private gastroenterology clinic (Masoud Clinic) from January 2011 to January 2014. Patients were visited and assessed clinically by endosonographer for one of the following reasons: suspicion for a mass or cyst in the pancreas or bile ducts, assessment of submucosal lesions found during esophagogastroduodenal endoscopy, or to rule out bile duct stones. Based on history and clinical assessment, if the endosonographer had a suspicion of pancreatic mass, the patient was asked to participate in the study. This invitation was made based on clinical suspicion and before endosonography was done. Cases and controls were selected according to the results of history taking, clinical exams, EUS, histopathology, and other information obtained during data collections. The endosonographer tried to take at least 30 times needle pass for obtaining the pancreatic tissue. If the endosonographer could not take enough tissue, the tissue was taken through fine needle aspiration (FNA) under computed tomography (CT) guide. The pancreatic tissue samples obtained during EUS were assessed by two expert pathologists. Finally, cases were those with a pathology report of pancreatic ductal adenocarcinomas.

Controls were selected from patients who referred for EUS, and the results indicated normal pancreas. After obtaining informed consent, the patients were referred to a trained general practitioner for interview.

Questionnaire data

Trained general practitioners administered a structured questionnaire with 113 questions to each study participant. The questionnaire was completed before the endosonography procedure for two reasons: (1) the physicians and the patients were unaware of the final diagnosis; therefore, the chance of interviewer or responder bias was minimized; and (2) the patients could respond to questions more accurately before receiving sedation for endosonography. The domains included in this questionnaire were demographic variables; anthropometric indices; socioeconomic status indicators; signs and symptoms of the current disease; occupational history and exposure to certain physical and chemical agents; medical and drug history; family history of cancer; history of consumption of alcohol, tobacco, or opium; history of tea and coffee consumption; pregnancy and menstrual data (only for women); and dietary habits and cooking methods. This questionnaire was tested for and showed excellent validity and reliability [16].

Assessment of dietary items

As mentioned, a structured questionnaire was used during face to face interview for all study subjects (n=629) [16]. Questions on nutrition and dietary habits consisted of the usual frequency of consumption of following food items: red meat, chicken, fish, bread, rice, tea, fruits, vegetables, and dairy products (including milk, yoghurt, cheese and yogurt drink) over a year preceding the disease. These items were asked according to the serving consumption multiplied by times per day, week, month, season, or year. The food servings were explained for every participant based on the national food items album [17]. All values were later converted to times per week, and in the case of red meat, chicken, and fish, the values were converted to time per day. To evaluate the cooking methods, the participants were asked for their typically used methods for cooking different foods (e.g. pan frying or sautéing, deep frying, grilling or barbecuing, and boiling for cooking different types of food).

Statistical method

All data were analyzed using SPSS 19.0 software package. All reported p-values are from two-sided tests and relative to a significance level of 5 %. The Kolmogorov–Smirnov statistic was used to test normality for all continuous variables. χ^2 test was used to compare ordinal data between groups.

The cumulative frequency of various food item intake dependent on the target variable was categorized into two, three, or four groups, based on the frequency of the intakes. Binary logistic regressions were used to estimate odds ratios (ORs) of PC and the corresponding 95 % confidence intervals (CIs) in the highest food item intake frequency compared with the first (lowest) category that acted as the reference category. For variables with three or more category, we reported *p for trend* (which was obtained based on considering the median value of each category of frequency of dietary intakes as a continuous variable to test for linear trends across categories), but for other variables, we presented *p*-value.

The first model did not include any adjustment, and only the association between the main variable and PC risk was tested. The latter model included adjustment for gender (male, female), age (40, 41–55, 56–70, 71–85, 86), BMI (kg/m^2) (18.49, 18.5–24.9, 25–29.9, 30), years of education (0 [illiterate], 5, 6–8, 9–12, university degree), history of diabetes (yes, no based on medical history), alcohol history (having used at least weekly for a period of 6 months or more: yes, no), smoking status (1, having used at least weekly for a period of 6 months or more: yes, no; 2, current smoker: yes, no, never), and opium use (having used at least weekly for a period of 6 months or more: yes, no).

Results

Demographic and known PC risk factors of 302 cases and 322 controls are shown in Table 1. No statistically significant differences were observed between cases and controls for age, years of education, and BMI. Compared with controls, the number of male subjects, current smokers, individuals with a history of diabetes, cigarette smoking, alcohol drinking, and opium use were higher in the case group (p-value<0.005) (Table 1).

The ORs and corresponding 95 % CIs for PC according to intake frequencies of the various food items are summarized in Table 2. After adjustment for gender, age, BMI, years of education, diabetes, alcohol history, smoking status, and opium use, a significant direct relationship was observed between PC risk and intake frequency (time/week) of bread (OR=1.50; 95 % CI 1.05–2.13; *p*-value: 0.024), rice (OR=2.10; 95 % CI 1.15–3.82; *p for trend* 0.034), and red meat (*OR*=2.25; 95 % CI 1.22–4.14; *p for trend* 0.033) (time/day), when comparing the highest category of intake frequency with the lowest.

In the first model, a positive association was observed between risk of PC and increased frequency of intake of "*yogurt drink*" (OR=1.35, 95 % CI 0.92–1.98; *p for trend* 0.033); however, this association was not significant in the fully

Table 1 Baseline characteristics of patients with pancreas cancer and control subjects

Characteristic		Controls (*n*=322) *N* (%)	Cases (*n*=307) *N* (%)	*p*-value
Gender	Male	144 (44.7)	180 (58.6)	0.00
	Female	178 (55.3)	127 (41.4)	
Body mass index[a]	Underweight (18.49)	13 (4)	11 (3.6)	0.09
	Normal (18.5–24.99)	102 (31.7)	126 (41)	
	Overweight (25–29.99)	141 (43.8)	111 (36.2)	
	Obese (30)	66 (20.5)	59 (19.2)	
Age (year)	27–59	114 (35.4)	98 (31.9)	0.61
	60–70	106 (32.9)	103 (33.6)	
	71–89	102 (31.7)	106 (34.5)	
Level of education	0 (illiterate)	133 (41.3)	136 (44.3)	0.74
	Primary (5)	73 (22.7)	59 (19.2)	
	Middle school (6–8)	31 (9.6)	35 (11.4)	
	High school (9–12)	49 (15.2)	42 (13.7)	
	University degree	36 (11.2)	35 (11.4)	
History of diabetes	Yes	56 (17.4)	86 (29.3)	0.001
	No	265 (82.6)	208 (70.7)	
Cigarette smoking[a]	Yes	84 (26.1)	104 (33.9)	0.03
	No	238 (73.9)	203 (66.1)	
Opium use[a]	Yes	20 (6.2)	50 (16.3)	0.00
	No	302 (93.8)	257 (83.7)	
Current smoker	Yes	33 (10.2)	46 (15)	0.05
	No	242 (75.2)	230 (75.2)	
	Never	47 (14.6)	30 (9.8)	
Alcohol drinking[a]	Yes	8 (2.5)	38 (12.4)	0.00
	No	314 (97.5)	268 (87.6)	

[a] Defined according to the World Health Organization as weight (kg)/height (m)^2, it was estimated using the weight before involuntary weight loss (especially in cases)

[b] Having used at least weekly for a period of 6 months or more

Table 2 Odds ratio and 95 % confidence interval for pancreatic cancer cases and control subjects according to quartile, tertiles, and categories of intake frequency of red meat, chicken, fish, bread, rice, fruit, milk, yoghurt, cheese, and "yogurt drink"

Food item frequency	Mean	Cases/controls	Model 1[a] OR (95 % CI)	Model 2[b] OR (95 % CI)
Bread (time per week)				
≤7	6.8	113/149	1.00	1.00
>7	18.4	187/170	1.45 (1.05–1.99)	1.50 (1.05–2.13)
p-value			0.023	0.024
Rice (time per week)				
<4	2.6	99/111	1.00	1.00
5.0–7.0	6.9	161/183	0.98 (0.69–1.39)	1.01 (0.69–1.47)
14.0–21.0	14.4	44/25	1.97 (1.12–3.45)	2.10 (1.15–3.82)
p for trend			0.034	0.034
Red meat (time per day)				
<0.7	0.3	49/68	1.00	1.00
1.0–1.6	1.0	55/73	1.04 (0.63–1.73)	1.33 (0.76–2.32)
2.0–3.0	2.5	148/137	1.49 (0.97–2.31)	1.77 (1.07–2.89)
>4.0	6.2	55/38	2.00 (1.15–3.49)	2.25 (1.22–4.14)
p for trend			0.030	0.033
Chicken (time per day)				
<1.2	0.8	76/77	1.00	1.00
2.0–3.0	2.5	158/162	0.98 (0.67–1.45)	0.89 (0.59–1.35)
>4.0	6.5	73/80	0.92 (0.59–1.44)	0.8 (0.49–1.30)
p for trend			0.92	0.67
Fish (time per day)				
<0.1	0.0	93/78	1.00	1.00
0.2–0.9	0.3	102/142	0.60 (0.40–0.89)	0.55 (0.35–0.85)
1.0–7.0	1.8	111/99	0.94 (0.62–1.4)	0.93 (0.59–1.47)
p for trend			0.016	0.009
Fruit (time per week)				
<4.0	2.0	105/79	1.00	1.00
5.0–7.0	7.0	140/187	0.56 (0.39–0.81)	0.56 (0.37–0.85)
>14.0	15.8	55/54	0.76 (0.47–1.23)	0.81 (0.47–1.38)
p for trend			0.008	0.018
Milk (time per week)				
<0.9	0.1	82/85	1.00	1.00
1.0–6.0	2.1	100/124	0.83 (0.55–1.24)	0.87 (0.56–1.36)
7.0<	7.8	124/112	1.14 (0.77–1.70)	1.27 (0.78–1.98)
p for trend			0.23	0.18
Yoghurt (time per week)				
<3.0	1.7	91/114	1.00	1.00
4.0–7.0	6.7	169/189	1.12 (0.79–1.58)	1.22 (0.83–1.79)
>14.0	14.4	45/18	3.13 (1.69–5.77)	3.95 (2.04–7.65)
p for trend			0.001	0.00
Cheese (time per week)				
<3.0	1.7	66/56	1.00	1.00
4.0–6.0	4.5	7/13	0.45 (0.17–1.22)	0.36 (0.12–1.09)
7.0–14.0	7.1	230/252	0.77 (0.52–1.15)	0.78 (0.50–1.20)
p for trend			0.21	0.16
"Yogurt drink" (time per week)				
<1.0	0.6	109/146	1.00	1.00

Table 2 (continued)

Food item frequency	Mean	Cases/controls	Model 1[a] OR (95 % CI)	Model 2[b] OR (95 % CI)
1.2–3.0	2.5	104/85	1.63 (1.12–2.39)	1.57 (1.04–2.36)
4.0<	7.5	91/90	1.35 (0.92–1.98)	1.32 (0.87–1.99)
p for trend			0.033	0.08

OR odds ratio, *CI* confidence interval

[a] Food item frequency analyses in first model without any adjustment

[b] Food item frequency analyses in second model which was adjusted adjustment for gender (male, female), age (≤40, 41–55, 56–70, 71–85, ≥86), BMI (kg/m^2) (18.49, 18.5–24.9, 25–29.9, ≥30), years of education (0 (illiterate), ≤5, 6–8, 9–12, university degree), history of diabetes(yes, no based on medical history), alcohol history (having used at least weekly for a period of 6 months or more: yes, no), smoking status (1, having used at least weekly for a period of 6 months or more: yes, no; 2, current smoker: yes, no, never), and opium use (having used at least weekly for a period of 6 months or more: yes, no)

adjusted model. No significant differences were found for intake frequency of chicken, milk, and cheese both in two models of analysis. In addition, increasing frequency of fish consumption was significantly associated with a reduced risk of PC (OR=0 .93; 95 % CI 0.59–1.47; *p for trend* 0. 009) (OR=0.81; 95 % CI 0.47–1.38; *p for trend* 0.018) in the first and second models, respectively.

The associations of different cooking methods with the risk of PC were further analyzed, as shown in Table 3. After adjustment for confounding variables mentioned above and frequency of each food item, increasing consumption of barbecuing red meat and deep frying of vegetables was associated with 67 % and 70 % increased risk of PC, respectively (*p*-value 0.025 and 0.006, respectively).

A reverse association was emerged between pan frying of vegetable (OR=0 .63, 95 % CI 0.44–0.90; *p*-value 0.011) and boiling of fish (OR=0.46, 95 % CI 0.23–0.91; *p*-value 0.026) in comparison with deep frying and barbeque cooking of fish and vegetable.

Discussion

The results of this case–control study demonstrate that increased frequency intake of bread, rice, and red meat are associated with a significantly increased risk of PC. In contrast, increased frequency intake of fruits and fish are associated with a significantly reduced risk of PC. Furthermore, barbecuing of red meat and frying of vegetables and fish were associated with increased risk of PC.

Since Iranian people would like toasted cereals such as rice and bread, the positive association between rice and bread intake and risk of PC might be due to high amounts of acrylamide in these food items, which are supposed to play role in pancreatic cancer pathogenesis [18].

We have also found a positive association between high frequency of red meat intake especially barbecued meat and PC risk, which could be explained by the high amounts of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) in these food items. PAH is a carcinogen type A which is mostly associated with smoking and cooking methods such as barbecuing and grilling [19–24]. A recent case–control study reported an increased risk of PC associated with high intakes of various HCAs [25]. Furthermore, several epidemiologic studies have observed positive associations with consumption of grilled and barbecued meat with risk of PC [26–30].

In this study, higher frequency of fish intake especially boiled fish was associated with lower risk of PC. Previous studies have reported controversial results for the association between fish intake and PC risk, which might be due to different types of fish consumed and/or fish preparation methods [31–34].

We found that deep fried vegetable intake is associated with increased risk of PC, which contradicts with raw vegetable use [35–41]. In this case–control study, we found an inverse association between frequency of fruit intake and PC risk, which is in line with the results of other case–control studies [37, 40]; however, prospective studies have reported imprecise associations because of small numbers of cases [35, 39, 41].

A recent meta-analysis of 14 cohort studies reported no association between consumption of dairy foods, calcium, or vitamin D during adulthood and PC risk [42], whereas a case–control study showed that fats found in dairy products increase risk of developing PC [43].

This study has some limitations; as with other case–control studies, a recall bias was inevitable. To avoid the probability that cases may recall their diets differently after PC diagnosis, we selected controls from the same patients who referred for endosonography with the same clinical signs and symptoms; however, using the same clinic controls, who may have different dietary habits and lifestyle when compared with the general population, is another limitation of this study. Furthermore, we are not entirely able to rule out residual confounding due to

Table 3 Odds ratio and 95 % confidence interval of different cooking methods for different food items in pancreatic cancer cases and control subjects

Cooking method		Cases/controls	Model 1[a] OR (95 % CI)	Model 2[b] OR (95 % CI)
Pan frying/sautéing				
Vegetables	No	159/136	1.00	1.00
	Yes	148/186	0.68 (0.49–0.93)	0.63 (0.44–0.90)
	p-value		0.016	0.011
Red meat	No	235/246	1.00	1.00
	Yes	72/76	0.95 (0.65–1.38)	1.03 (0.68–1.55)
	p-value		0.78	0.88
Fish	No	215/246	1.00	1.00
	Yes	92/76	1.48 (1.03–2.14)	1.55 (1.04–2.31)
	p-value		0.034	0.028
Deep frying				
Vegetables	No	195/234	1.00	1.00
	Yes	112/88	1.52 (1.1–2.14)	1.70 (1.16–2.48)
	p-value		0.016	0.006
Red meat	No	272/291	1.00	1.00
	Yes	35/31	1.11 (0.66–1.86)	1.16 (0.66–2.04)
	p-value		0.69	0.58
Grilling/barbecuing				
Red meat	No	192/187	1.00	1.00
	Yes	115/135	1.83 (1.22–2.75)	1.67 (1.06–2.64)
	p-value		0.003	0.025
Fish	No	277/299	1.00	1.00
	Yes	30/23	1.33 (0.74–2.38)	1.22 (0.64–2.33)
	p-value		0.32	0.53
Boiling				
Vegetables	No	216/249	1.00	1.00
	Yes	91/73	1.44 (1.00–2.07)	1.33 (0.90–1.98)
	p-value		0.045	0.14
Red meat	No	109/112	1.00	1.00
	Yes	198/210	0.96 (0.69–1.34)	0.91 (0.63–1.30)
	p-value		0.81	0.61
Fish	No	291/287	1.00	1.00
	Yes	16/35	0.46 (0.25–0.86)	0.46 (0.23–0.91)
	p-value		0.01	0.026

OR odds ratio, *CI* confidence interval

[a] Cooking methods for different food items analyses in first model which was only adjusted for each food item frequency of intake

[b] Cooking methods for different food items analyses in second model which was adjusted for gender (male, female), age (≤40, 41–55, 56–70, 71–85, ≥86), BMI (kg/m^2) (18.49, 18.5–24.9, 25–29.9, ≥30), years of education (0 (illiterate), ≤5, 6–8, 9–12, university degree), history of diabetes (yes, no based on medical history), alcohol history (having used at least weekly for a period of 6 months or more: yes, no), smoking status (1, having used at least weekly for a period of 6 months or more : yes, no; 2, current smoker: yes, no, never), and opium use (having used at least weekly for a period of 6 months or more: yes, no)

inevitable imprecise measurement or the omission of unknown covariates; however, we tried to do our best in measurement of all variables and adjustment for all known covariates. Also, nonsignificant associations may have been declared significant by chance alone.

In conclusion, this study provides some evidence for the association between frequency of food item intake and their cooking methods with risk of PC development; however, more studies are still needed to be able to conclude.

Conflict of interest ZGh, AH, HEZ, SF, RR, RM, and AP declare no conflict of interest related to this work.

Ethics statement The authors declare that the survey was performed in a manner that conforms to the Declaration of Helsinki of 1975, as revised in 2000 and 2008, concerning human and animal rights and that the authors followed the policy concerning informed consent wherever applicable as shown in www.Springer.com.

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