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The relationship between new-onset diabetes mellitus and pancreatic cancer risk: A case–control study

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ABSTRACT

Diabetes mellitus (DM) is widely considered to be associated with pancreatic cancer, however, whether DM is a cause or consequence of pancreatic cancer is controversial. In the present study, 1458 patients with pancreatic ductal adenocarcinoma (PDAC) and 1528 age-, sex- and sociodemographic variables-matched controls were recruited in two university-affiliated hospitals from 1st January 2000 to 31st December 2009. DM was defined as fasting blood glucose (FBG) level of 7.0 mmol/L or greater. An unconditional multivariable logistic regression analysis was used to estimate adjusted odds ratios (AORs) and 95% confidence interval (CI). Compared with controls, a moderate increased risk of PDAC was observed among cases with long-standing diabetes (⩾2-year duration), with an AOR (95% CI) of 2.11 (1.51–2.94). Interestingly, a significant higher risk was observed among cases with new-onset DM (<2-year duration), with an AOR of 4.43 (3.44–5.72) compared to controls without DM. In addition, we found a synergistic interaction between cigarette smoking and DM on modifying the risk of pancreatic cancer development (AOR = 6.17, 95% CI 3.82–9.94). Similarly, a synergistic interaction between new-onset DM and family history of pancreatic cancer was found for pancreatic cancer risk, with an AOR (95% CI) of 11.04 (2.51–48.53). This study suggested that DM could be both an early manifestation of pancreatic cancer and an aetiologic factor. Possible effect modification on DM by family history of pancreatic cancer and smoking status should be further explored in future aetiologic studies.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC), commonly known as pancreatic cancer, is a serious medical and public health problem.[1] In Europe, pancreatic cancer is the fifth cause of cancer death in men and the sixth in women.[2,3] To explore the effective tools for early diagnosis of this disease, identification of individuals at high risk for pancreatic cancer would provide a significant impact on reducing pancreatic cancer morbidity and mortality. However, little is known about the risk factors for pancreatic cancer, except for age and cigarette smoking.

The association between diabetes mellitus (DM) and the development of pancreatic cancer has long been recognised

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since 1833.[4] In most epidemiological studies, patients were defined as having DM if they reported previous diagnosis of DM or if the diagnosis was documented in their medical records. The prevalence of pancreatic cancer-associated DM in these studies is about 20%.[5] On the other hand, about 45–65% patients meet the criteria for DM at the time of cancer to be diagnosed, evaluated with either oral glucose tolerance test or fasting blood glucose (FBG) measurement according to the World Health Organization criteria[6] or FBG measurement using the American Diabetes Association criteria (ADA).[7] There is a moderately increased risk of pancreatic cancer in people with long-standing diabetes[8,9] and a significant high increased rate of pancreatic cancer diagnosis was observed in people with new-onset DM.[10,11] Recent studies showed that more than half of the patients with pancreatic cancer-associated DM was new-onset, which was defined as DM reported less than 2 years' duration.[12–15] Importantly, a close temporal association has been observed between the onset of DM and the diagnosis of pancreatic cancer.[12,14]

If DM individuals at the highest risk for pancreatic cancer could be identified through epidemiologic studies, targeted surveillance of this population might potentially identify pancreatic cancer at early stage. A recent study by Chari et al. [10] found that patients with new-onset DM have a 3-year risk of developing pancreatic cancer nearly eight times higher than a person of similar age and sex without diabetes. However, this study cannot quantify the modification of other risk factors in defining a higher risk population for having pancreatic cancer among subjects with new-onset DM, because of the limited number of pancreatic cancer subjects with new-onset DM ($n = 18$).[10]

In our present case–control study, the first aim was to evaluate the association between PDAC risk and DM (especially new-onset DM) after adjusting potential modifiable factors, such as age, smoking, family history of pancreatic cancer and alcoholic consumption in Chinese Han people. The second aim was to more precisely assess the possible interactions between these risk factors for PDAC.

2. Materials and methods

2.1. Study population

The study design was an ongoing hospital-based case–control study conducted at two university-affiliated hospitals (Ruijin hospital and Changhai hospital, Shanghai, China) between 1st January 2000 and 31st December 2009. The purpose of the study was to define environmental factors that contribute to the development of PDAC. The study protocol was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained from all patients. Totally, there were 2329 potential pancreatic cancer patients during the study period and 1707 patients with histologically confirmed primary pancreatic ductal adenocarcinoma. The most common reason for patients not to obtain a histologic diagnosis was old age because elderly patients often opted to have no treatment for their cancer. Excluded patients were those who at baseline (1) did not receive a FBG test or were missing glucose data ($n = 88$); (2) had concurrent cancer at another organ site or past history of cancer ($n = 127$); and (3) were unable or unwilling to give informed consent ($n = 34$). The remaining 1458 patients were enrolled in this study (Fig. 1). Eligible patients were all Han people of Chinese inhabitant. Control subjects consist of patients admitted to the same hospitals at the same time for any acute conditions based on their discharge diagnoses. Patients and controls were matched by age (±5 years), sex and sociodemographic variables. Patients with any other malignant diseases were excluded. In addition, cases related to alcohol and tobacco consumption (e.g., respiratory diseases, peptic ulcer and hepatic disease) were also excluded based on discharge diagnoses. There were a total of 1528 controls in this study.

2.2. Data collection

Patients and controls were personally interviewed by trained medical doctors, who collected information on demographics and other risk factors for pancreatic cancer (such as smoking history, alcohol consumption, medical history and family history of pancreatic cancer). No proxy interview was involved.

Smokers were defined as individuals who had smoked more than 100 cigarettes in their lives. Daily alcohol consumption was estimated based on answers to questions regarding the type, duration and frequency of alcoholic drinks. These answers were integrated into a scoring system which was used to classify alcohol consumption as 'low or moderate' (0–30 g/day) or 'heavy' consumption ($\geqslant$30 g/day). Family history of pancreatic cancer was restricted to first-degree or second-degree relatives. Serum glucose measurements were obtained under fasting or postprandial conditions for routine clinical purposes. DM was defined as criteria of FBG levels greater than 7.0 mmol/L or postprandial blood sugar exceeded 11.1 mmol/L or a previous diagnosis of DM, according to ADA criteria. The course of DM was calculated from the date of diagnosis of DM to the date of pancreatic cancer diagnosis. For those diagnosed on admission, the course was recorded as less than 2 years. Duration of DM was dichotomised at 2 years to define cases of DM as new-onset DM or long standing. The cutoff at 2 years was set according to that PDAC progressing was so rapidly that it was unlikely a case of PDAC-induced DM would go without cancer detection for more than 2 years.[16] Based on ADA criteria, impaired fasting glucose (IFG) was defined as FBG level

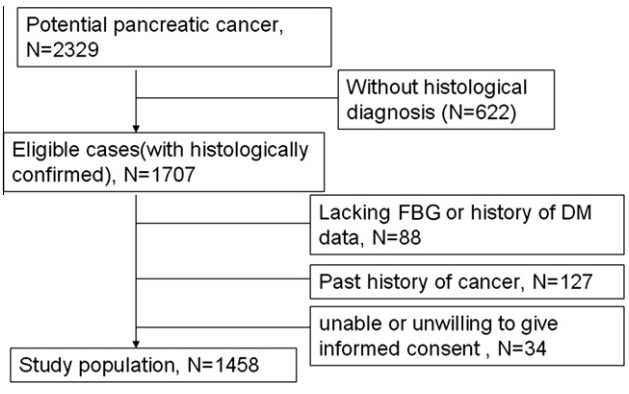

Fig. 1 – Flowchart of patient selection. FBG, fasting blood glucose; DM, diabetes mellitus.

⩾5.6 mmol/L and <7.0 mmol/L and normal fasting glucose (NFG) was defined as FBG level <5.6 mmol/L.

2.3. Statistical analysis

All statistical analyses were conducted using the PASW Statistics 18.0 software program (SPSS, Chicago, IL, USA). Cases and controls were compared by chi-square test, Fisher's exact probability for categorical variables or Student's *t*-test for continuous variables. Crude and adjusted odds ratios (AOR) and 95% confidence intervals (CI) for each variable were calculated by using unconditional logistic regression. Potential confounders were included in the multivariate analysis performed in a stepwise manner at a significant level of $p < 0.15$. Equations included terms for age, family history of pancreatic cancer, history of DM, smoking status and alcohol drinking. Interaction terms were tested as candidate variables in the logistic regression model. To assess deviation from the additive model, S (synergy index) = (OR11 − 1)/(OR01 + OR10 − 2), where OR11 = odds ratio of the joint effect of two risk factors and OR01 and OR10 = OR of each risk factor in the absence of the other. All tests were two-tailed and a p value <0.05 was considered to be significant.

3. Results

3.1. Subject characteristics

The demographic characteristics of the 1458 cases and 1528 controls included in this study are presented in Table 1. No significant differences in sex, residence and education levels were observed between cases and controls, suggesting that the frequency matching was adequate. However, a significant difference in the distribution of age in the case group was observed compared with the control group ($p < 0.001$).

3.2. Prevalence of DM in the PDAC group and control group

Among the 1458 patients, 403 (27.6%) were diabetic. There were 151 diabetic patients in the control group, with an incidence of 9.9%. The percentage of patients with DM was significantly higher in the case group compared to control group ($p < 0.001$, Fig. 2). IFG (FBG level of 5.6–6.9 mmol/L) was present in 436 cases and 338 controls (29.9% versus 22.1%, $p < 0.001$). Overall, only 42.6% of patients with pancreatic cancer had normal FBG level as compared with 68% of controls ($p < 0.001$). The percentage of patients with a new-onset diabetic course (<2-year duration) was significantly higher in the case group compared to the control group (20.9% versus 5.8%, $p < 0.001$). In addition, the frequency distribution of DM in the controls in the current study was similar to that in Shanghai, China, as recorded in a population-based study[17] ($p = 0.154$, data not shown), indicating that our controls were highly representative.

3.3. Associations between DM and pancreatic cancer risk

To estimate associations between DM and other factors with pancreatic cancer risk, unconditional logistic regression analysis was used (Table 2). Because demographic factors (except for age) for cases and controls were comparable, we chose to present the ORs after adjusting for age, smoking status, diabetes, alcohol consumption and family history of pancreatic cancer. After adjustment for the above-mentioned variables, the ORs (95% CI) of risk for pancreatic cancer associated with the smoking status, alcohol consumption, DM and family history of pancreatic cancer were 1.58 (1.28–1.95), 0.99 (0.78–1.26), 3.47 (2.82–4.27) and 2.00 (1.34–3.01), respectively.

We further analysed the risk of pancreatic cancer in correlation with the duration of DM. Compared with subjects

Table 1 – Demographic characteristics of the study population.

Variable	Cases $n = 1458$ (%)	Controls $n = 1528$ (%)	p Value
Age (mean ± SD)	62.5 ± 10.0	61.8 ± 8.2	<0.001*
⩽40	39(2.7)	30(2.0)	
41–50	218(15.0)	238(15.6)	
51–60	433(29.7)	459(30.0)	
61–70	507(34.8)	621(40.6)	
71–80	233(16.0)	175(11.5)	
⩾81	28(1.9)	5(0.3)	
Gender			0.644**
Male	982(67.4)	1017(66.6)	
Female	476(32.6)	511(33.4)	
Education levels			0.157**
Elementary school or less	101(6.9)	127(8.3)	
Middle or high school	817(56.0)	871(57.0)	
College or higher level of education	507(34.8)	489(32.0)	
Missing data	33(2.3)	41(2.7)	
Residents			0.565**
Rural residents	489(33.5)	507(33.2)	
Urban residents	947(65.0)	1016(66.5)	
Missing data	22(1.5)	5(0.3)	

Note: Student's *t*-test (*), Pearson's χ^2 test (**) were used, respectively.

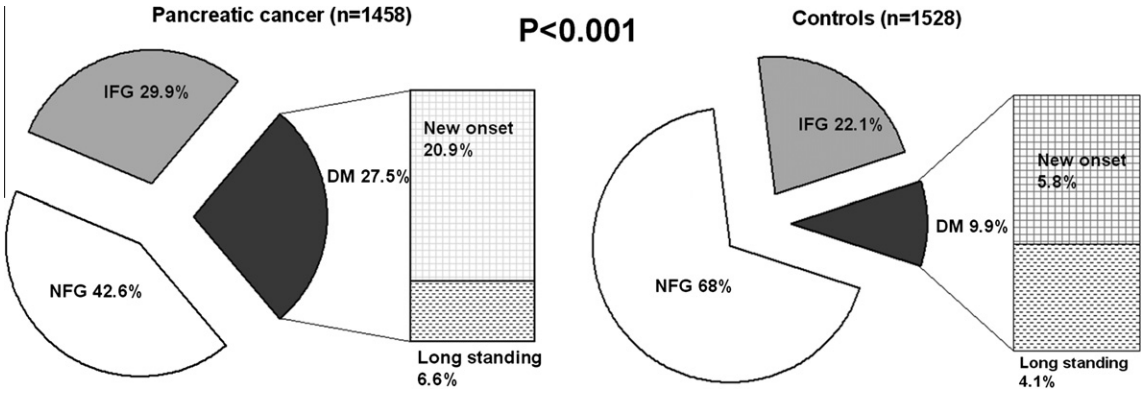

Fig. 2 – Frequency distribution of FBG among pancreatic cancer cases (*n* = 1458) and controls (*n* = 1528). NFG was defined as FBG level <5.6 mmol/L; IFG was defined as FBG level ⩾5.6 mmol/L and <7.0 mmol/L; DM was defined as FBG level ⩾7 mmol/L or postprandial blood sugar exceeded 11.1 mmol/L or a previous diagnosis of DM, according to ADA criteria. The course of DM was calculated from the date of diagnosis of DM to the date of diagnosis of pancreatic cancer. Duration of DM was dichotomised at 2 years to define cases of DM as new-onset DM. NFG, normal fasting glucose; IFG, impaired fasting glucose; FBG, fasting blood glucose; DM, diabetes mellitus.

Table 2 – Effect of potential factors for pancreatic cancer risk in multivariable logistic regression analysis.

	Cases *n* = 1458 (%)	Controls *n* = 1528 (%)	AOR (95.0% CI)[a]	*p*
Alcohol drinking				
No/moderate	1099(75.4)	1278(83.6)	1	
Heavy	310(21.3)	250(16.4)	0.99(0.78–1.26)	0.947
Missing data	49(3.3)	0(0)		
Smoking				
No	942(64.6)	1179(77.2)	1	
Yes	516(35.4)	349(22.8)	1.58(1.28–1.95)	<0.001
Family history of pancreatic cancer				
No	1315(90.1)	1489(97.4)	1	
Yes	87(6.0)	39(2.6)	2.00(1.34–3.01)	0.001
Missing data	56(3.8)	0(0)		
Diabetes mellitus				
No	1055(72.4)	1377(90.1)	1	
Yes	403(27.6)	151(9.9)	3.47(2.82–4.27)	<0.001
New-onset(<2 years)	307(20.9)	88(5.8)	4.43(3.44–5.72)	<0.001
Long-standing(⩾2 years)	96(6.6)	63(4.1)	2.11(1.51–2.94)	<0.001

AORs, adjusted odds ratios; CI, confidence interval.
[a] Adjusted by age, smoking status, alcohol drinking, history of diabetes and family history of pancreatic cancer.

without DM, patients having new-onset DM had an AOR (95% CI) of 4.43 (3.44–5.72). Nevertheless, only a figure-elevated risk was observed between long-standing DM (⩾2 years) and pancreatic cancer risk (AOR = 2.11, 95% CI 1.51–2.94).

3.4. *Interaction between DM and other risk factors*

Next, we examined the associations between risk factors for PDAC, such as cigarette smoking and family history of pancreatic cancer in cases and controls in relation to DM (Table 3). We found that cigarette smokers with DM had an adjusted OR (95% CI) of 6.17 (3.82–9.94), compared with non-smokers without DM. In addition, patients with both new-onset DM and a family history of pancreatic cancer had an 11-fold higher risk (AOR, 11.04, 95% CI 2.51–48.53) of PDAC, compared with those who had neither a family history of pancreatic cancer nor a history of DM. Using the AORs as an estimate for the relative risk of disease development, the relative excess risk for patients with a history of DM, along with smoking or a family history of pancreatic cancer, exceeded the sum of the relative excess risks for each risk factor alone [for example, 6.17–1.0 > (3.12–1.0) + (1.62–1.0)]. The estimated synergism index (S) was 1.9, 1.0 and 2.4 for smoking/diabetes-, smoking/new-onset DM- and new-onset DM/family history of pancreatic cancer-interaction, respectively. This indicated that the joint effect of cigarette smoking, the history of DM and the family history of pancreatic cancer are superadditive. No significant interaction was observed between other risk factors, such as age, heavy alcohol consumption with cigarette smoking, DM or family history of pancreatic cancer.

Table 3 – Interactive effects of smoking, DM and family history of pancreatic cancer.

		Cases	Controls	AOR[a] (95% CI)	*p*
DM	Smoking				
No	No	673	1052	1	
No	Yes	382	325	1.62(1.29–2.03)	<0.001
Yes	No	260	127	3.12(2.46–3.94)	<0.001
Yes	Yes	143	24	6.17 (3.82–9.94)	<0.001
Smoking	New-onset DM				
Yes	No	297	221	1.59 (1.23–2.05)	<0.001
No	Yes	196	68	4.39 (3.28–5.89)	<0.001
Yes	Yes	93	18	4.77(2.71–8.38)	<0.001
New-onset DM	Family history of pancreatic cancer				
No	No	959	1340	1	
No	Yes	63	37	1.77 (1.15–2.74)	0.01
Yes	No	266	86	4.38 (3.38–5.67)	<0.001
Yes	Yes	18	2	11.04 (2.51–48.53)	0.01

AORs, adjusted odds ratios; CI, confidence interval; DM, diabetes mellitus.
S (synergy index) = (OR11 – 1)/(OR01 + OR10 – 2), where OR11 = odds ratio of the joint effect of two risk factors and OR01 and OR10 = OR of each risk factor in the absence of the other.
[a] AOR = odds ratio adjusted for age, history of diabetes, family history of pancreatic cancer, heavy alcohol consumption and smoking status.

4. Discussion

In the present study, we found a positive association between DM and the risk of developing pancreatic cancer. This positive association was independent of other known and suspected pancreatic cancer risk factors (such as cigarette smoking and heavy alcohol drinking). In addition, we revealed that new-onset DM had an increased risk for pancreatic cancer. Importantly, we demonstrated a novel finding that new-onset DM had a significant synergistic interaction with the family history of pancreatic cancer on PDAC risk.

Several epidemiologic studies have reported a positive association between DM and pancreatic cancer risk.[8,18] However, information on the epidemiologic characteristics of pancreatic cancer-associated DM in Han Chinese is limited. In the present case–control study of 1458 PDAC patients and 1528 age- and sex-matched controls, we found that the overall prevalence of DM in cases was 27.6%, significantly higher compared to non-cancer controls. Of these pancreatic cancer-associated DM, the duration of the DM less than 2 years (new-onset) was shown in 76.2%, which was significantly higher than controls. Our findings were similar with the recent study by Pannala et al., who found that DM was more prevalent (47% versus 7%; $p < .001$) and predominantly of new onset (74% versus 53%; $p = 0.002$) among cases compared with controls.[19] This time-course characteristic strongly supported the hypothesis that DM might be a consequence of PDAC. Recent studies also suggested that pancreatic cancer-associated DM is likely a unique form of DM that is caused by the cancer. This is supported by the following findings: DM occurs with a high frequency and in close temporal association with the diagnosis of pancreatic cancer[12,14]; and DM improves after resection of the tumour of pancreas.[19,20] The mechanisms by which pancreatic cancer leads to DM are not clear. Several lines of evidences have indicated that pancreatic cancer-associated DM does not depend on the destruction of pancreatic beta cells[21], but rather, on the development of peripheral insulin resistance.[22] Various hypotheses about the mode of action of these factors have been proposed. On a cellular level, blockage of insulin receptors as well as impaired insulin action and glucose transport has been demonstrated to be involved in pancreatic cancer-associated insulin resistance.[23,24] Furthermore, pancreatic cancer extracts can interfere with glycogen synthesis in isolated muscle cells.[25]

Recently, the result from a meta-analysis indicated that the combined age- and sex-adjusted OR for pancreatic cancer-associated DM was 1.8 (95% CI, 1.7–1.9). In addition, subjects with DM duration of 4 years or less had a 50% greater risk of pancreatic cancer compared with subjects with DM duration of 5 years or more.[9] Similar results were also obtained from North America.[12] In the present study, we also found an association between DM and increased risk of pancreatic cancer compared with those without DM (AOR = 3.27, 95% CI, 2.66–4.1). When stratifying the duration of DM as new-onset DM or long-standing DM, the former was found to have a higher increased risk for pancreatic cancer than those with long-standing DM [AOR (95% CI), 4.43 (3.44–5.72) versus 2.11 (1.51–2.94)]. The current estimation of the overall risk of pancreatic cancer supports previous work that has identified an inverse temporal relationship between DM and pancreatic cancer risk.[8,26]

The most notable findings of the present study were the interactions among their factors for pancreatic cancer. A significant synergistic effect was found between a positive family history of pancreatic cancer and new-onset DM, though the mechanisms were unknown. One of the hypotheses may be attributable to gene–environment interaction. It has been demonstrated that the risk of PDAC is exceptionally high among individuals with a strong family history of pancreatic cancer.[27] Studies by Lichtenstein and colleagues suggested that the aggregation of PDAC in some families had a genetic basis, although the gene or genes responsible for familial PDAC have not yet been identified.[28] We assume that subjects carrying these unknown gene or genes may be susceptible to develop DM when they are attacked by PDAC. To our knowledge, this is the first research on interactions between

new-onset DM and other risk factors for PDAC, and it merits further study in the future. We also found a synergistic effect between smoking and DM for pancreatic cancer risk. This may be explained by the fact that smoking-induced oxidative stress increases patients' susceptibility to chronic inflammation, DNA damage and pancreatic cancer development.[29] Additivity was further demonstrated between smoking and new-onset DM, which further provided evidences from another angle to confirm that, although long-standing diabetes was an aetiologic factor for pancreatic cancer, new-onset diabetes was a manifestation of the cancer.

The strengths of this study are represented as follows: (1) high number of pancreatic cancer patients; (2) high homogeneity of the series of tumours. Only patients with histologically confirmed pancreatic ductal adenocarcinoma were included; (3) adequate size of the control group; (4) high representative of control group, the prevalence of DM among our controls is consistent with those of other Chinese Han population-based research; (5) both cases and controls belonged to a relatively homogeneous base population, who were matched by sex, age and sociodemographic variables. Bias should be minimised by the matching. Moreover, the enrollment of cases and controls at the same units and during the same time frame may also limit at least partially the inherent biases of case–control studies. Nevertheless, this study also has some limitations. First, we cannot completely avoid the possibility of selection bias due to the use of in-patient controls, which may have overestimated or underestimated the prevalence of DM among control subjects. However, it is less likely that our finding of the positive relationship between new-onset diabetes and pancreatic cancer risk is confounded by selection bias for the following reasons: (1) people admitted to the same hospitals for any acute conditions, not accompanying any cancers or conditions related to alcohol and tobacco consumption, were selected as controls, in order to reduce the possibility of biasing results. (2) A number of inclusion and exclusion criteria for our control group were set. We think that a selection bias due to this procedure would be rather unlikely. Second, recall of past diagnoses may be biased, which may be different among cases and controls. Recall error of duration of DM could have led to a bias towards the null. Third, our study did not obtain subclassification data on the type of diabetes. Given the older age of our population of pancreatic cancer patients and more than 90% of DM were type 2 DM in china, the vast majority of patients in our cohort likely belong to type 2 rather than insulin-dependent (type I) diabetes. In addition, despite age-matched cases and controls, the difference in the mean age was still significant, which might increase the selection bias to some extent. Albeit it is not possible to avoid completely any bias, we think that the results are not chance findings. Caution is needed in interpreting the results since the case and control features limit their generalisation.

In conclusion, our data support the recently reported positive association between new-onset DM and PDAC risk. In addition, new-onset DM may have a significant synergistic interaction with a family history of pancreatic cancer on PDAC risk. These findings merit further confirmation in a larger population-based prospective study in the future.

Conflict of interest statement

None declared.

REFERENCES

1. Ghaneh P, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer. *Gut* 2007;**56**(8):1134–52.
2. Bosetti C, Bertuccio P, Levi F, et al. Cancer mortality in the European Union, 1970–2003, with a joinpoint analysis. *Ann Oncol* 2008;**19**(4):631–40.
3. Ferlay J, Parkin DM. Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010;**46**(4):765–81.
4. Arnquist HJ, Bright R. Cases and observations connected with disease of the pancreas and duodenum. *Med Chir Tr* 1833;**18**:1–56.
5. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, et al. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer* 2007;**120**(9):1986–92.
6. World Health Organization. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation*. Geneva, Switzerland: World Health Organization; 2006.
7. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2007;**30**(Suppl. 1):S42–7.
8. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 1995;**273**(20):1605–9.
9. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005;**92**(11):2076–83.
10. Chari ST, Leibson CL, Rabe KG, et al. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 2005;**129**(2):504–11.
11. Gupta S, Vittinghoff E, Bertenthal D, et al. New-onset diabetes and pancreatic cancer. *Clin Gastroenterol Hepatol* 2006;**4**(11):1366–72 [quiz 1301].
12. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology* 2008;**134**(1):95–101.
13. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* 2009;**10**(1):88–95.
14. Pannala R, Leibson CL, Rabe KG, et al. Temporal association of changes in fasting blood glucose and body mass index with diagnosis of pancreatic cancer. *Am J Gastroenterol* 2009;**104**(9):2318–25.
15. Chari ST, Klee GG, Miller LJ, Raimondo M, DiMagno EP. Islet amyloid polypeptide is not a satisfactory marker for detecting pancreatic cancer. *Gastroenterology* 2001;**121**(3):640–5.
16. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009;**137**(2):482–8.
17. Jia WP, Pang C, Chen L, et al. Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. *Diabetologia* 2007;**50**(2):286–92.
18. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer* 2003;**89**(3):519–23.

19. Pannala R, Leirness JB, Bamlet WR, et al. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* 2008;**134**(4):981–7.
20. Ohtsuka T, Kitahara K, Kohya N, Miyoshi A, Miyazaki K. Improvement of glucose metabolism after a pancreatoduodenectomy. *Pancreas* 2009;**38**(6):700–5.
21. Basso D, Millino C, Greco E, et al. Altered glucose metabolism and proteolysis in pancreatic cancer cell conditioned myoblasts: searching for a gene expression pattern with a microarray analysis of 5000 skeletal muscle genes. *Gut* 2004;**53**(8):1159–66.
22. Permert J, Ihse I, Jorfeldt L, et al. Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer. *Br J Surg* 1993;**80**(8):1047–50.
23. Liu J, Knezetic JA, Strommer L, et al. The intracellular mechanism of insulin resistance in pancreatic cancer patients. *J Clin Endocrinol Metab* 2000;**85**(3):1232–8.
24. Isaksson B, Strommer L, Friess H, et al. Impaired insulin action on phosphatidylinositol 3-kinase activity and glucose transport in skeletal muscle of pancreatic cancer patients. *Pancreas* 2003;**26**(2):173–7.
25. Basso D, Valerio A, Brigato L, et al. An unidentified pancreatic cancer cell product alters some intracellular pathways of glucose metabolism in isolated rat hepatocytes. *Pancreas* 1997;**15**(2):132–8.
26. Wang F, Gupta S, Holly EA. Diabetes mellitus and pancreatic cancer in a population-based case–control study in the San Francisco Bay Area, California. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(8):1458–63.
27. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004;**64**(7):2634–8.
28. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;**343**(2):78–85.
29. Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: case–control study. *Am J Gastroenterol* 2007;**102**(12):2696–707.