Hyperglycemia as a risk factor in pancreatic cancer: a nested case-control study using prediagnostic blood glucose levels

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Research

Keywords: Pancreatic ductal adenocarcinoma, hyperglycemia, pancreatic cancer, risk

Posted Date: September 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-76139/v1

Version of Record: A version of this preprint was published at Pancreatology on May 1st, 2021. See the published version at https://doi.org/10.1016/j.pan.2021.05.008.

Abstract

Background: To determine the risk association between fasting glucose levels and pancreatic cancer using systematically collected prediagnostic blood glucose samples

Methods: Prospective nested case-control study of participants from the Northern Sweden Health and Disease Study, including 182 cases that developed pancreatic cancer and four matched controls per case. Blood glucose levels, at fasting and after an oral glucose tolerance test, collected up to 24 years before pancreatic cancer diagnosis were analyzed. The association between fasting glucose levels and pancreatic cancer risk was determined using unconditional and conditional logistic regression models and trend analysis. The association between fasting glucose and the time to pancreatic cancer diagnosis, tumor stage and survival was determined using a likelihood-ratio test, t-test and log-rank test.

Results: The unadjusted risk of developing pancreatic cancer increased with increasing fasting glucose levels (OR 1.30, 95% CI 1.05-1.60, $P = .015$). Impaired fasting glucose (≥6.1 mmol/L) was associated with an adjusted risk of 1.77 for developing pancreatic cancer (95% CI 1.05-2.99, $P = .032$). The risk association was strongest in never-smokers (OR 4.02, 95% CI 1.26-12.77) and non-diabetics (OR 3.08, 95% CI 1.08-4.79). Fasting glucose levels were not associated with TNM stage at diagnosis or survival.

Conclusions: High fasting glucose is associated with an increased risk of developing pancreatic cancer and the risk association is stronger in never-smokers and non-diabetics.

Introduction

Pancreatic ductal adenocarcinoma (pancreatic cancer) has a five-year survival rate of 9% [1]. Most patients are diagnosed with metastatic disease due to late presenting symptoms and only 10–20% are able to undergo surgery with a curative intent [2]. Radiologic screening for pancreatic cancer is recommended for individuals at high risk, including certain hereditary conditions, rare syndromes and pancreatic cysts [3, 4].

Diabetes mellitus is common in pancreatic cancer patients. At diagnosis, only 14% have a normal fasting glucose and nearly half have diabetes mellitus [5]. Surgical resection improves the glycemic status, suggesting that the primary tumor contributes to diabetes development [5, 6]. This is supported by experimental data in mice, where pancreatic cancer cell injection causes impaired glucose regulation [7]. Sharma et al. recently showed that hyperglycemia appears 30–36 months before pancreatic cancer diagnosis [6]. Another study examined prediagnostic radiology and glucose levels and found that tumors are generally resectable at the time of diabetes diagnosis [8]. While individuals with newly diagnosed diabetes have been suggested as a potential group to screen for pancreatic cancer [9], this strategy has not been tested. We hypothesized that glucose homeostasis is altered early in pancreatic cancer development and that glucose measurements may identify risk groups. This study aimed to characterize fasting glucose alterations prior to pancreatic cancer diagnosis and to determine the risk association between hyperglycemia and pancreatic cancer.

Methods

Study design

We designed a prospective nested case-control study using data from the ongoing Northern Sweden Health and Disease Study (NSHDS). The NSHDS is a cohort study where the general population is invited to health examinations. The data include survey information, lab tests and a biobank with biological samples from three sub-cohorts (described in detail at https://cedcd.nci.nih.gov/cohort?id=44).

We identified NSHDS participants that were subsequently diagnosed with pancreatic cancer in the Swedish cancer registry between January 1990 and December 2016. We used medical records to include only individuals with pancreatic ductal adenocarcinoma verified by histology or cytology. We excluded individuals with an uncertain diagnosis and those without records of fasting glucose, oral glucose tolerance tests (OGTT) or diabetes status. Controls without any cancer diagnosis were selected from the NSHSD. We matched four controls to each case survey by gender, age at participation (± one year) and date of participation (± three months).

Data collection from NSHDS and medical records

The collected prediagnostic survey data included fasting glucose, glucose after OGTT, body mass index (BMI), blood pressure and self-reported diabetes diagnosis, tobacco use and alcohol consumption. Plasma samples were drawn after overnight fasting. OGTT was performed according to World Health Organization standards, with plasma glucose levels measured at 120 minutes after a 75 g oral glucose load. The methods of glucose analysis differed slightly over time, i.e. capillary vs. venous samples and different bench-top analyzers. Patients previously diagnosed with diabetes or with fasting glucose that exceeded the criterion for diabetes did not generally undergo OGTT.

Additional clinical data were collected on the pancreatic cancer cases from medical records, including fasting glucose at diagnosis (measured at the time of diagnosis ± three months), TNM stage, tumor grade, survival after diagnosis and treatment.

Definitions

Diabetes mellitus was defined according to WHO standards: fasting plasma glucose ≥ 7.0 mmol/L or an OGTT with venous plasma glucose ≥ 11.1 mmol/L or capillary plasma glucose ≥ 12.2. Impaired fasting glucose was defined as fasting plasma glucose ≥ 6.1 mmol/L. Impaired glucose tolerance was defined as venous plasma glucose ≥ 7.8 mmol/L or capillary plasma glucose ≥ 8.9 mmol/L after OGTT [10].

To set similar time frames for resectable and non-resectable disease, the time of pancreatic cancer diagnosis was defined as the date of the first radiological finding of a suspected primary tumor or metastases. Survival was defined as the time between the date of diagnosis and the date of death. Previous diabetes was defined as a documented diabetes diagnosis in medical records, self-reported diabetes in the survey data or having prescribed diabetes medication. Diabetes duration prior to pancreatic cancer diagnosis was defined as the time between diabetes onset as above or the start of

diabetes medication if no onset date was documented. Diabetes was defined as new-onset if diagnosed within three years before the pancreatic cancer diagnosis [11].

Statistical analysis

We used STATA 14 (Stata corp., College Station, TX, USA) and Prism 7 (GraphPad Software, San Diego, CA, USA) for statistical analyses and graph construction. Odds ratios stratified by time intervals were calculated using multiple logistic regression models with levels of fasting glucose or glucose after OGTT as continuous variables. The time intervals were based on previous definitions of new-onset diabetes. The interaction between fasting glucose and time to diagnosis on pancreatic cancer risk was evaluated using a likelihood-ratio test. Conditional logistic regression models, conditioning on individual case set, were used to calculate odds ratios when fasting glucose values were categorized according to WHO definitions of hyperglycemia. These models were adjusted for age, gender, glucose measurement method and confounders. Trends were calculated in a separate model using a base 2 logarithm of the fasting glucose value. Odds ratios stratified by known risk factors were calculated in a logistic regression model using a base 2 logarithm of fasting glucose values. For cases participating in more than one survey only the fasting glucose measurement from the last survey occasion was used in logistic regression models. All unconditional logistic regression models were adjusted for the blood glucose analysis method. Survival analysis was performed using Kaplan-Meier curves and a log rank test. *P*-values of < .05 were considered significant throughout this study.

Results

Study population

Of 302 eligible cases, 182 were included in the analysis after various exclusions (Fig. 1). Seventy-four cases had participated more than once (two times: n = 46, three times: n = 10, four times: n = 12, five times: n = 4, six times: n = 2), with a total of 310 surveys. Most cases were matched with four control surveys (96%). Hospital record data for the included cases are presented in Table 1 and survey data from cases and controls (last survey before pancreatic cancer diagnosis) are presented in Table 2. Approximately three percent of the cases had diabetes at the time of the last survey occasion (Table 2) compared with ~ 30% at the time of pancreatic cancer diagnosis (Table 1). Smoking was more common among cases than controls in NSHDS surveys, but there were no differences in mean BMI, alcohol consumption and the proportion with a diabetes diagnosis between the groups (Table 2). Glucose levels were measured up to 24 years before pancreatic cancer diagnosis. The distribution is shown in Supplementary Fig. 1.

Table 1
Clinical data for all included pancreatic cancer cases.

Variable (n, %)		All cases (n = 182)
Gender	Male	111 (61.0%)
	Female	71 (39.0%)
Age at pancreas cancer diagnosis	Mean (95% confidence interval)	64.2 (63.0-65.5)
Diagnosed with diabetes at pancreatic cancer diagnosis	Yes	54 (29.7%)
	No	122 (67.0%)
	Unknown	6 (3.3%)
Diabetes onset	New-onset (≤ three years prior to pancreatic cancer diagnosis)	28 (15.4%)
	Long standing	10 (5.5%)
	After pancreatic cancer diagnosis	8 (4.4%)
	Unknown	8 (4.4%)
Previous other cancer diagnosis	Yes	4 (2.2%)
	No	178 (97.8%)
Surgical treatment	No surgery	123 (67.6%)
	Curative resection	31 (17.0%)
	Palliative surgery	27 (14.8%)
	Unknown	1 (0.5%)
Tumor localization	Head	107 (58.8%)
	Body	39 (21.4%)
	Tail	20 (11.0%)
	Unknown	16 (8.8%)
TNM stage	IA - IB	10 (5.5%)
	IIA - IIB	29 (15.9%)
	III	18 (9.9%)
	IV	110 (60.4%)
	Unknown	15 (8.2%)
Dead		173 (95.1%)

Variable (n, %)		All cases (n = 182)
Median survival (months)	All stages	6.6
	Stage I	20.7
	Stage II	10.7
	Stage III	7.9
	Stage IV	4.8

Table 2
Survey data from Northern Sweden Health and Disease Study.

	Cases n = 182	Controls n = 717
Years to pancreatic cancer diagnosis Median (range)	7.0 (0.1–24.2)	-
Age groups (%) <45 years 45–55 years >55 years	10.4% 19.2% 70.3%	10.5% 19.5% 70.0%
Diabetes diagnosis at survey occasion (%) Yes N.A.	3.4% 2.2%	3.2% 1.0%
BMI Mean (95% CI) N.A. (%)	26.3 (25.8–26.9) 0.5%	26.5 (26.2–26.8) 0.4%
Alcohol (%) Non-consumer N.A.	14.8% 18.1%	17.3% 12.1%
Smoking (%) Smoker Former smoker Never smoker N.A.	29.4% 23.2% 47.5% 2.7%	16.1% 26.5% 57.4% 2.1%
Abbreviations: N.A. = Not available. BMI = Body mass Index. CI = Confidence interval		

Fasting glucose levels prior to pancreatic cancer diagnosis

Over time, fasting glucose increased more steeply in cases compared with matched controls (Fig. 2A) in an interaction model adjusted for age (p = .009). In addition, mean fasting glucose levels were significantly higher in cases at both 0–3 and 3–6 years prior to the cancer diagnosis compared with

controls (Supplementary Fig. 2). Fasting glucose levels at diagnosis were available for comparison with the prediagnostic fasting glucose levels in 51 non-diabetic cases. Prediagnostic mean fasting glucose levels increased over time and were above the limit for impaired fasting glucose (≥ 6.1 mmol/L) at six years prior to pancreatic cancer diagnosis and above the limit for diabetes diagnosis (≥ 7.0 mmol/L) at the time of pancreatic cancer diagnosis (Fig. 2B).

The association between pancreatic cancer risk and fasting glucose in non-diabetics was determined (n = 165). We observed a higher overall odds ratio (OR) for developing pancreatic cancer with each mmol/L increase in fasting glucose level (OR 1.30, 95% CI 1.05–1.60, *P* = .02). The risk association between fasting glucose and pancreatic cancer analysis was then stratified by the lag time between sampling and pancreatic cancer diagnosis. The odds ratio for a lag time of between 3 and 6 years before diagnosis was significantly increased (1.49, 95% CI 1.05–2.10, *P* = .02), while the odds ratio for 0–3 years before diagnosis approached significance (1.47, 95% CI 0.99–2.19, *P* = .06) (Fig. 2D). A test for interaction showed no association between lag time and pancreatic cancer development (*P* = .5). When the analyses were repeated using OGTT values, there were no differences between cases and controls at any of the time intervals (Supplementary Fig. 3).

Fasting glucose levels in association with body mass index, tumor stage and survival

The majority of both cases and controls were above the age of 55 (Table 2). As pancreatic cancer develops in the late decades of life, this subgroup (age ranging between 55 to 71 years) was used to correlate fasting glucose with BMI, tumor stage and survival. Approximately 50% of cases and controls were overweight, with no significant difference between the groups (mean BMI 26.5 vs. 26.7 kg/m^2, *P* = .77). BMI was not associated with an increase in the odds ratio for pancreatic cancer (OR 0.99, 95% CI 0.95–1.03, *P* = .58). Cases had higher mean fasting glucose levels after adjusting for BMI compared with controls (*P* = .004) and mean fasting glucose was higher in relation to BMI for cases (Fig. 3A). We investigated this relationship further using the ratio between fasting glucose and BMI. The OR for pancreatic cancer was 1.66 (95% CI 1.04–2.66, *P* = .034) for each 0.1 increase in the fasting glucose to BMI ratio.

Pancreatic cancer survival was not affected by having impaired fasting glucose or diabetes within six years prior to the pancreatic cancer diagnosis (*P* = .56) (Fig. 3B). Similarly, having diabetes at pancreatic cancer diagnosis did not affect survival (*P* = .49) (Supplementary Fig. 4). We found no difference in fasting glucose levels between cases with metastatic pancreatic cancer (Stage IV) compared with those with less advanced stages (Stages I-III) (Fig. 3C). Comparing Stage I-II vs. Stage III-IV did not alter the results (data not shown).

Hyperglycemia and risk of pancreatic cancer development

We then assessed the risk of developing pancreatic cancer in individuals aged 55 years or older, stratified by their fasting glucose level and analyzed independent of the time between sampling and diagnosis. The survey data for this group are summarized in Supplementary Table 1. Cases were more likely to have

impaired fasting glucose compared with controls, but there was no difference in manifest diabetes between the groups at the time of the survey.

Having impaired fasting glucose (≥ 6.1 mmol/L) was associated with an increased odds ratio for pancreatic cancer development in a conditional logistic regression model after adjusting for confounders that are associated with both pancreatic cancer risk and hyperglycemia (BMI, diabetes diagnosis and smoking status) (*P* for trend = .02) (Table 3). Logistic regressions stratified by risk factors are shown in Fig. 4. A doubling of fasting glucose was associated with an increased risk of pancreatic cancer among never-smokers (OR 4.02, 95% CI 1.26–12.77, *P* = .018) and non-diabetics (OR 3.08, 95% CI 1.08–4.79, *P* = .035).

Table 3
Odds ratios for pancreatic cancer at different fasting glucose level intervals among NSHDS participants older than 55 years.

Fasting glucose level (mmol/L)	Cases (n)	Controls (n)	OR (95% CI)	
			Unadjusted conditional risk analysis	Adjusted conditional risk analysis*
< 6.1	81	369	1 (ref)	1 (ref)
6.1-7.0	30	83	1.69 (1.03–2.77)	1.77 (1.05–2.99)
> 7.0	11	34	1.36 (0.64–2.86)	1.91 (0.73–5.03)
P for trend			0.16	0.021
Abbreviations: OR = Odds Ratio; CI = Confidence Interval				
*Adjusted for BMI, diabetes diagnosis and smoking status.				

Discussion

In this nested prospective case-control study, we found that elevated fasting glucose is associated with an increased pancreatic cancer risk and that impaired fasting glucose confers an especially high risk in never-smokers and non-diabetics. The study highlights impaired fasting glucose as an independent pancreatic cancer risk factor. In addition, fasting glucose levels are not affected by the presence of distant metastasis and are not associated with pancreatic cancer mortality.

We found that impaired fasting glucose is an independent risk factor for pancreatic cancer in individuals > 55 years of age. Both diabetes mellitus and smoking are established strong risk factors for pancreatic cancer based on multiple studies and meta-analyses [12]. Here, we show that individuals that have never smoked and individuals that have not been diagnosed with diabetes run an increased risk of pancreatic cancer if their fasting glucose is impaired. This finding has important implications for the characterization of high- vs low-risk individuals for pancreatic cancer. We also show that the relation

between BMI and fasting glucose differs for individuals that subsequently develop pancreatic cancer since mean fasting glucose levels are higher in relation to BMI. Possibly, other factors than the metabolic syndrome drive hyperglycemia in individuals that develop pancreatic cancer. Indeed, we found that an increased ratio between fasting glucose and BMI is associated with an increased risk for pancreatic cancer.

Pannala et al. showed that pancreatic cancer patients are 26 times more likely to have diabetes at the time of diagnosis compared with individuals without cancer [5]. It has been estimated that the hyperglycemic status among pancreatic cancer patients is initiated 30–36 months prior to the cancer diagnosis, whereas the limit for a diabetes diagnosis is reached approximately 6–12 months prior to cancer diagnosis [6]. The same study reported that patients with large resectable tumors had a prediagnostic fasting glucose comparable to that of patients with unresectable tumors. It was speculated that the similarity was related to metastatic burden, in turn affecting the glycemic profile [6]. By contrast, we found that the prediagnostic glycemic profile was independent of TNM stage, suggesting that hyperglycemia is affected by tumor presence rather than tumor burden or metastasis.

It is possible that the high prevalence of hyperglycemia and diabetes observed at pancreatic cancer diagnosis represents a different pathophysiology than the modest elevation in fasting glucose that precedes diagnosis by several years. One subset of patients might be more insulin resistant, with concomitantly increased insulin secretion from the beta cells, promoting local anabolic effects that accelerate tumor progression from premalignant lesions. The long-term association with risk should mark an etiological aspect of pancreatic cancer incidence, linked, for example, to elevated insulin levels that may constitute the causal factor linking obesity with pancreatic cancer incidence [13]. We did expect to find a stronger relationship between fasting glucose and pancreatic cancer risk with a shorter lag time between sampling and diagnosis, since reverse causation has previously been postulated. There was no significant increase in risk in the last three years prior to diagnosis. This possibly constitutes a type II error, due to a fairly small number of cases within that time frame.

The impact of diabetes on survival after resected early-stage pancreatic cancer has rendered inconclusive results in previous studies [5, 14–16]. In our study cohort, having manifest diabetes at the time of cancer diagnosis did not affect survival. Nor did we find any difference in survival between patients that were hyperglycemic vs. patients that were normoglycemic in the six years prior to diagnosis.

Screening for pancreatic cancer must focus on risk groups with a reasonably high pre-test probability of pancreatic cancer development. Currently, pancreatic cancer screening by radiology is recommended for risk groups with more than a five-fold increase in risk, which include patients with certain pancreatic cysts, hereditary pancreatitis and familial pancreatic cancer [3, 4, 17]. However, all these are relatively rare conditions. The development of risk scores based on known risk factors, including impaired fasting glucose, might define additional individuals that would benefit from pancreatic cancer screening. Speculatively, risk group identification could be aided by additional biomarkers, reporting on the interplay between premalignant or early-stage pancreatic cancer and hyperglycemia. This interplay is not, however,

well understood. Hormonal alterations leading to insulin resistance are the favored hypothesis compared with local tumor effects on insulin production [18]. Experimental studies have found possible mediators of the paraneoplastic phenomenon, including adrenomedullin, islet amyloid polypeptide and exosomal micro-RNAs [7, 19, 20]. These mediators are interesting biomarker candidates for risk group identification.

Limitations to the present study include the geographic homogeneity of the study cohort, consisting of people living in the northern part of Sweden. There is a lack of reliable data on alcohol consumption, due mainly to changes in the questionnaire over time, which prevented us from adjusting for that potential confounder. There is also a possibility of selection bias towards a healthier study population, which might contribute to the low prevalence of diabetes in the surveys. A high BMI is a proposed risk factor for pancreatic cancer [18, 19], but, in our study, BMI was not associated with pancreatic cancer risk. However, this is likely not due to selection bias, as the percentage of overweight individuals in our study corresponds well with that in the general Swedish population. In addition, the NSHDS cohort has a high participation rate, with only marginal social selection bias, and can be regarded as a cohort with high external validity [21].

To summarize, this nested case-control study shows that fasting glucose levels are associated with pancreatic cancer risk. Impaired fasting glucose in individuals aged > 55 is associated with an increased risk and especially in non-diabetics and never-smokers. Impaired fasting glucose is an independent risk factor and should be investigated as a potential marker for pancreatic cancer risk assessment.

List Of Abbreviations

NSHDS	Northern Sweden Health and Disease Study
OGTT	oral glucose tolerance test
BMI	body mass index
OR	Odds ratio

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 and was approved by the regional ethical review board in Umeå (2016/384-31). Individual need for approval was waived.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was funded by grants from the medical faculty at Umeå University (223-1828-13 for Oskar Franklin), Bengt Ihres Foundation (SLS-885861), the Claes Groschinsky Memorial Foundation (M 19391), Lions Cancer Research Foundation, Umeå University (LS 18-140 for Sara Jacobson), the Swedish Research Council (2016-02990 and 2019-01690 for Malin Sund), the Swedish Cancer Society (CAN 2016-643 and 19027 for Malin Sund), the Sjöberg Foundation (for Malin Sund) and Region Västerbotten (RV-837731 and RV 930132 for Oskar Franklin. RV-841551 and RV-583411 for Malin Sund). The funders had no role in the design of the study, data collection, data analysis, interpretation of data or in writing the manuscript.

Specific author contributions

SJ: Acquisition of data, analysis and interpretation of data, drafting of the manuscript and statistical analysis. Approval of the final version of the manuscript
OF: Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Approval of the final version of the manuscript
PD: Study concept and design, writing and critical revision of the manuscript for important intellectual content. Approval of the final version of the manuscript
MJ: Study concept and design. Statistical analysis, critical revision of the manuscript for important intellectual content. Approval of the final version of the manuscript
JS: Study concept and design. Statistical analysis, critical revision of the manuscript for important intellectual content. Approval of the final version of the manuscript
OB: Study concept and design. Interpretation of data. Critical revision of the manuscript for important intellectual content. Approval of the final version of the manuscript
MS: Study concept and design, study supervision, critical revision of the manuscript for important intellectual content. Approval of the final version of the manuscript

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they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Acknowledgements

Hanna Nyström, Erik Lundberg and Daniel Öhlund contributed to the data collection from medical records.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA: a cancer journal for clinicians 69(1) (2019) 7-34.

[2] S. Gillen, T. Schuster, C. Meyer Zum Buschenfelde, H. Friess, J. Kleeff, Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages, PLoS Med 7(4) (2010) e1000267.

[3] M.I. Canto, F. Harinck, R.H. Hruban, G.J. Offerhaus, J.W. Poley, I. Kamel, et al., International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer, Gut 62(3) (2013) 339-47.

[4] M. Del Chiaro, C.S. Verbeke, N. Kartalis, R. Pozzi Mucelli, P. Gustafsson, J. Hansson, et al., Short-term Results of a Magnetic Resonance Imaging-Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer, JAMA surgery 150(6) (2015) 512-8.

[5] R. Pannala, J.B. Leirness, W.R. Bamlet, A. Basu, G.M. Petersen, S.T. Chari, Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus, Gastroenterology 134(4) (2008) 981-7.

[6] A. Sharma, T.C. Smyrk, M.J. Levy, M.A. Topazian, S.T. Chari, Fasting Blood Glucose Levels Provide Estimate of Duration and Progression of Pancreatic Cancer Before Diagnosis, Gastroenterology 155(2) (2018) 490-500 e2.

[7] G. Aggarwal, V. Ramachandran, N. Javeed, T. Arumugam, S. Dutta, G.G. Klee, et al., Adrenomedullin is up-regulated in patients with pancreatic cancer and causes insulin resistance in beta cells and mice, Gastroenterology 143(6) (2012) 1510-1517 e1.

[8] M. Pelaez-Luna, N. Takahashi, J.G. Fletcher, S.T. Chari, Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis, The American journal of gastroenterology 102(10) (2007) 2157-63.

[9] R. Pannala, A. Basu, G.M. Petersen, S.T. Chari, New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer, The Lancet. Oncology 10(1) (2009) 88-95.

[10] W.H.O.I.D. Federation., Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia : report of a WHO/IDF consultation / World Health Organization, International Diabetes Federation., Geneva, Switzerland : World Health Organization2006.

[11] S.T. Chari, C.L. Leibson, K.G. Rabe, L.J. Timmons, J. Ransom, M. de Andrade, et al., Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer, Gastroenterology 134(1) (2008) 95-101.

[12] P. Maisonneuve, A.B. Lowenfels, Risk factors for pancreatic cancer: a summary review of meta-analytical studies, Int J Epidemiol 44(1) (2015) 186-98.

[13] R. Carreras-Torres, M. Johansson, V. Gaborieau, P.C. Haycock, K.H. Wade, C.L. Relton, et al., The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study, Journal of the National Cancer Institute 109(9) (2017).

[14] C.K. Chu, A.E. Mazo, M. Goodman, V. Egnatashvili, J.M. Sarmiento, C.A. Staley, et al., Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma, Annals of surgical oncology 17(2) (2010) 502-13.

[15] P.A. Hart, S.T. Chari, Diabetes mellitus and pancreatic cancer: why the association matters?, Pancreas 42(8) (2013) 1207-9.

[16] J. Kleeff, E. Costello, R. Jackson, C. Halloran, W. Greenhalf, P. Ghaneh, et al., The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer, British journal of cancer 115(7) (2016) 887-94.

[17] M. Del Chiaro, C. Verbeke, R. Salvia, G. Kloppel, J. Werner, C. McKay, et al., European experts consensus statement on cystic tumours of the pancreas, Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 45(9) (2013) 703-11.

[18] D. Li, Diabetes and pancreatic cancer, Mol Carcinog 51(1) (2012) 64-74.

[19] J. Permert, J. Larsson, G.T. Westermark, M.K. Herrington, L. Christmanson, P.M. Pour, et al., Islet amyloid polypeptide in patients with pancreatic cancer and diabetes, The New England journal of medicine 330(5) (1994) 313-8.

[20] L. Wang, B. Zhang, W. Zheng, M. Kang, Q. Chen, W. Qin, et al., Exosomes derived from pancreatic cancer cells induce insulin resistance in C2C12 myotube cells through the PI3K/Akt/FoxO1 pathway, Sci Rep 7(1) (2017) 5384.

[21] M. Norberg, S. Wall, K. Boman, L. Weinehall, The Vasterbotten Intervention Programme: background, design and implications, Global health action 3 (2010).

Figures

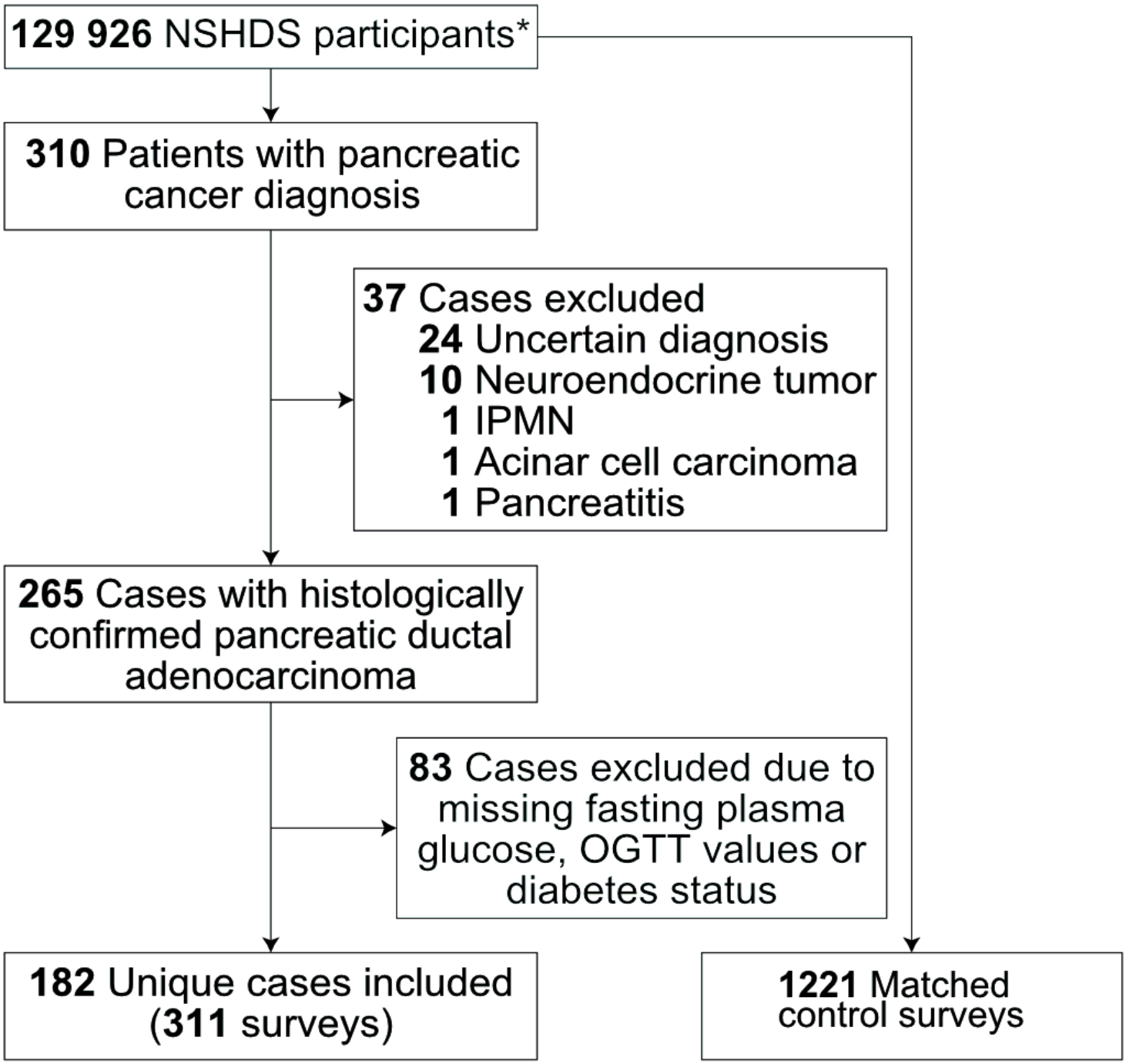

Figure 1

Study design and flowchart. Excluded cases are presented in the boxes to the right. Diagnosis was deemed uncertain if histopathological or cytological verification of pancreatic ductal adenocarcinoma was unavailable. NSHDS = Northern Sweden Health and Disease Study; OGTT = oral glucose tolerance test. *As of Jan 13, 2016

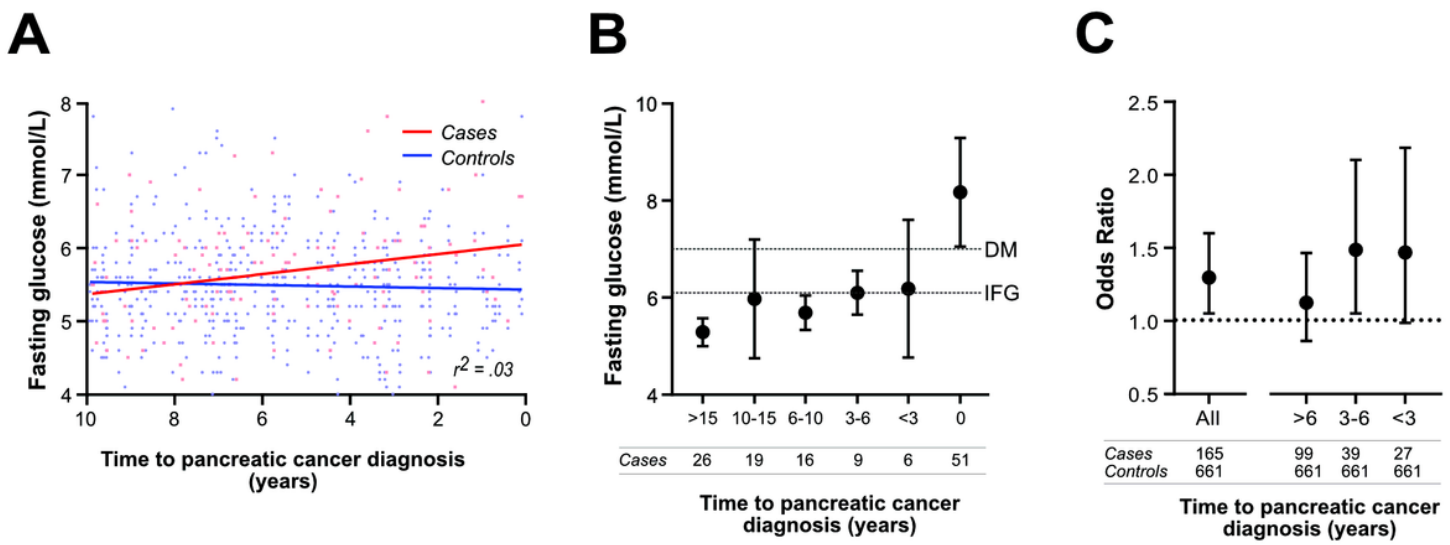

Figure 2

Analyses of fasting glucose preceding pancreatic cancer diagnosis. Error bars show 95% confidence intervals. A) Scatter plot and linear regression showing fasting glucose levels in relation to time left to cancer diagnosis among all cases and controls without a diabetes diagnosis. B) Mean fasting glucose levels before and at diagnosis for the subgroup of cases with fasting glucose measurements available at diagnosis. DM = diabetes mellitus; IFG = impaired fasting glucose. C) Odds ratios for pancreatic cancer in relation to fasting glucose levels stratified by time intervals prior to pancreatic cancer diagnosis. Cases and controls with diabetes diagnosis was excluded from the analysis. For cases participating in more than one survey only the fasting glucose measurement from the last survey occasion was used.

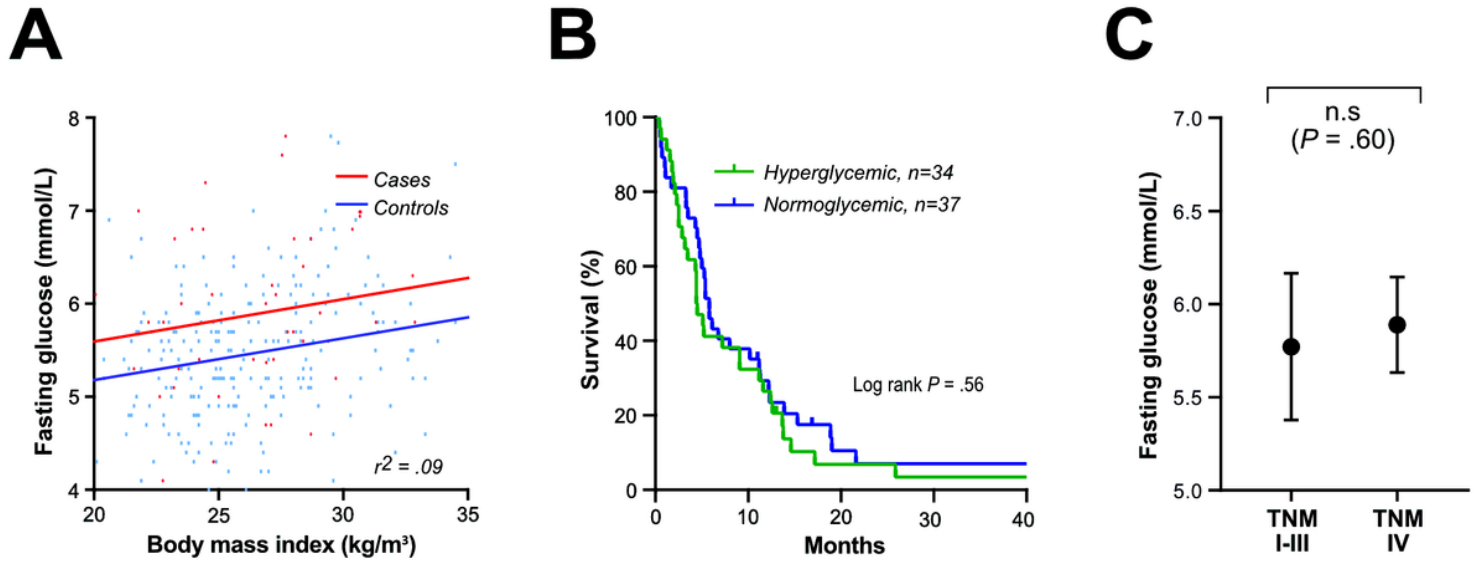

Figure 3

Prediagnostic fasting glucose in association with BMI, survival and TNM stage. Measurements within six years prior to diagnosis were included. A) Fasting glucose levels for cases and controls in relation to BMI.

Included measurements are from the last survey occasion of non-diabetic subjects older than 55 years. B) Kaplan-Meier curves for pancreatic cancer patients stratified into hyperglycemic (≥6.1 mmol/L) and normoglycemic groups (<6.1 mmol/L). All age groups included. C) Fasting glucose levels, mean and 95% confidence interval, subdivided according to TNM stage at diagnosis. Fasting glucose levels from non-diabetic patients older than 55 years were included. Error bars show 95% confidence intervals.

	Cases	Controls	OR	95 % CI
All	122	486	1.85	0.84 - 4.07
BMI<25	45	170	2.49	0.58 - 10.72
BMI>25	75	306	1.80	0.69 - 4.73
No diabetes	115	462	3.08	1.08 - 4.79
Diabetes	4	20	1.28	0.06 - 26.04
Never smoker	30	65	4.02	1.26 - 12.77
Former smoker	30	142	1.28	0.27 - 5.99
Smoker	58	266	0.86	0.15 - 4.83

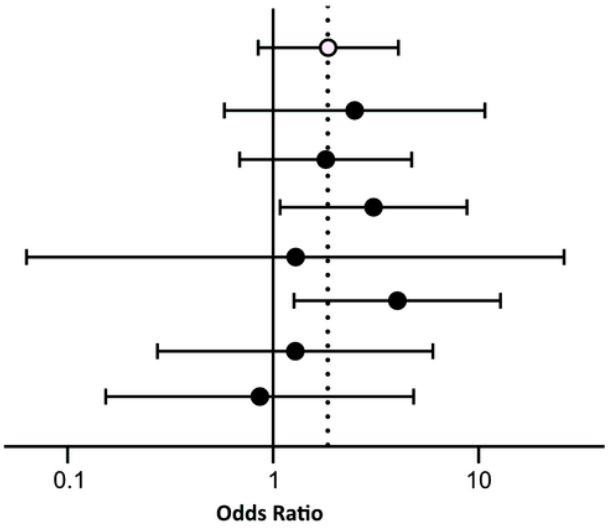

Figure 4

Forest plot. Odds ratio for pancreatic cancer development among subjects older than 55 years. Logistic regression models using a base 2 logarithm of prediagnostic fasting glucose levels measured at the last occasion of participation in NSHDS. Stratified for BMI level (< 25 kg/m2 vs. ≥ 25 kg/m2), diabetes diagnosis and smoking status. Error bars show 95% confidence intervals. The dashed vertical line indicates the calculated overall odds ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfiguresandtables.docx