Original Article

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

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ABSTRACT

Objective: 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 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. The association between fasting glucose and the time to pancreatic cancer diagnosis, tumor stage and survival was determined using 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). In subgroup analysis, fasting glucose levels were associated with an increased risk in never-smokers (OR 4.02, 95% CI 1.26—12.77, P = .018) and non-diabetics (OR 3.08, 95% CI 1.08—8.79, P = .035) (non-significant for interaction). The ratio between fasting glucose and BMI was higher among future pancreatic cancer patients and an increased ratio was associated with elevated risk of pancreatic cancer (OR 1.66, 95% CI 1.04—2.66, P = .034). Fasting glucose levels were not associated with TNM stage at diagnosis or survival.

Conclusions: High fasting glucose is associated with an increased risk of being diagnosed with pancreatic cancer.

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]. Although this is a well-known phenomenon, neither the underlying etiology nor the impact on prognosis have been established. Surgical resection improves the glycemic status, suggesting that the primary tumor contributes to diabetes development [5,6]. This is also 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

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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 impact of hyperglycemia on pancreatic cancer risk and survival.

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 NSHDS. 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 min 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. A linear regression model was used to illustrate fasting glucose levels over time within the last 10 years preceding pancreatic cancer detection. 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, i.e. BMI, diabetes mellitus diagnosis and smoking status. 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. P-values for effect modification were calculated using likelihood-ratio tests. For cases participating in more than one survey only the fasting glucose measurement from the last survey occasion was used in logistic regression models. We reasoned that it would be more likely to detect a clinically relevant risk association since pancreatic cancer usually presents after 60 years of age. 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.

Fasting glucose levels prior to pancreatic cancer diagnosis

Over time, fasting glucose increased more steeply in cases compared with matched controls (Fig. 2A) in a linear regression
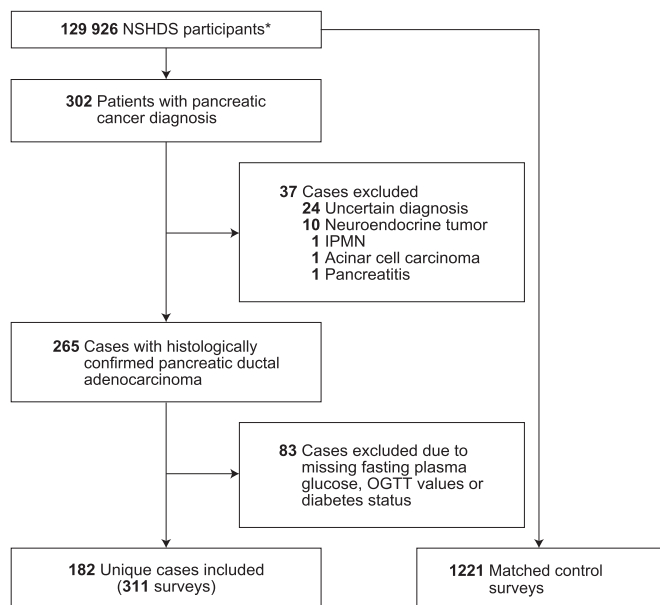
Fig. 1. Study design and flowchart. Excluded cases are presented in the boxes to the right. Diagnosis was deemed uncertain if histopathological or cytological verification of pancreatic ductal adenocarcinoma was unavailable. NSHDS = Northern Sweden Health and Disease Study; OGTT = oral glucose tolerance test. *As of Jan 13ʼ 2016.

model adjusted for age (*P* for interaction = .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 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, n = 39), while the odds ratio for 0–3 years before diagnosis approached significance (1.47, 95% CI 0.99–2.19, *P* = .06, n = 27) (Fig. 2C). 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 and 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/m², *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

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%)
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	7.0 (0.1 − 24.2)	−
Median (range)		
Age groups (%)	10.4%	10.5%
<45 years	19.2%	19.5%
45−55 years	70.3%	70.0%
>55 years		
Diabetes diagnosis at survey occasion (%)	3.4%	3.2%
Yes	2.2%	1.0%
N.A.		
BMI	26.3 (25.8 − 26.9)	26.5 (26.2 − 26.8)
Mean (95% CI)	0.5%	0.4%
N.A. (%)		
Alcohol (%)	14.8%	17.3%
Non-consumer	18.1%	12.1%
N.A.		
Smoking (%)	29.4%	16.1%
Smoker	23.2%	26.5%
Former smoker	47.5%	57.4%
Never smoker	2.7%	2.1%
N.A.		

Abbreviations: N.A. = Not available. BMI = Body mass Index. CI = Confidence interval.
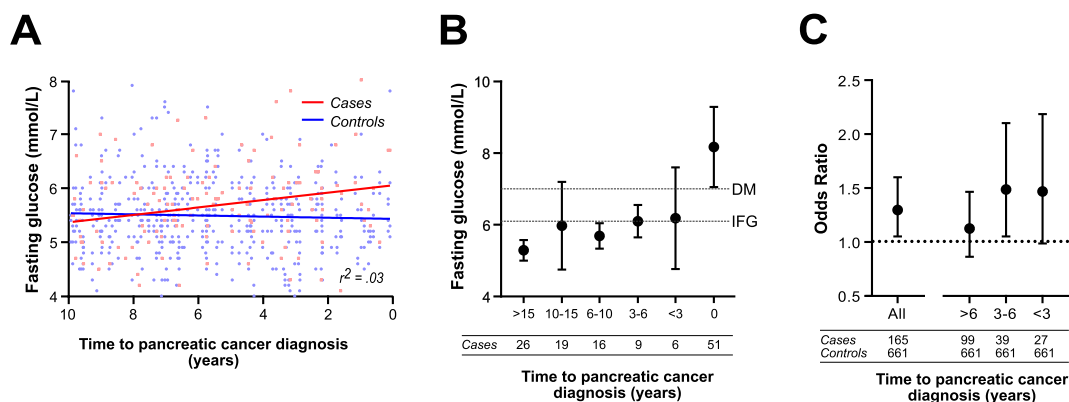

Fig. 2. Analyses of fasting glucose preceding pancreatic cancer diagnosis. Error bars show 95% confidence intervals. A) Scatter plot and linear regression showing fasting glucose levels in relation to time left to cancer diagnosis among all cases and controls without a diabetes diagnosis. B) Mean fasting 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.

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) and there was no significant difference when comparing long-standing and new-onset diabetes ($P = .40$) (Supplementary Fig. 5). 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 1.08−8.79, $P = .035$). However, there was no significant interaction in any of the stratified analyses (Fig. 4).

Discussion

In this nested prospective case-control study, we found that elevated fasting glucose is associated with an increased pancreatic cancer risk. Further, our results suggest that pancreatic cancer-
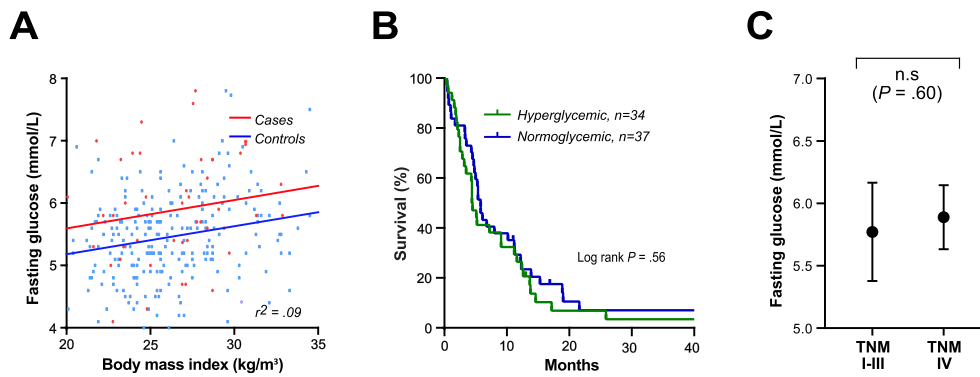
Fig. 3. Prediagnostic fasting glucose in association with BMI, survival and TNM stage. Measurements within six years prior to diagnosis were included. A) Fasting glucose levels for cases and controls in relation to BMI. Included measurements are from the last survey occasion of non-diabetic subjects older than 55 years. B) Kaplan-Meier curves for pancreatic cancer patients stratified into hyperglycemic ($\geq$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.

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[a]
<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			.16	.021

Abbreviations: OR = Odds Ratio; CI = Confidence Interval.
[a] **Adjusted for BMI, diabetes diagnosis and smoking status.**

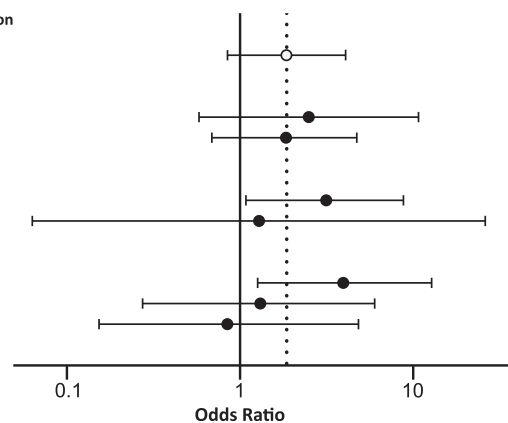|	Cases	Controls	OR (95% CI)	P for interaction
All	122	486	1.85 (0.84 - 4.07)	
BMI				.74
BMI<25	45	170	2.49 (0.58 - 10.72)	
BMI≥25	77	310	1.69 (0.65 - 4.44)	
Diabetes diagnosis				.63
No	115	462	3.08 (1.08 - 4.79)	
Yes	4	20	1.28 (0.06 - 26.04)	
Smoking status				.27
Never smoker	30	65	4.02 (1.26 - 12.77)	
Smoker	58	266	0.86 (0.15 - 4.83)	
Former smoker	30	142	1.28 (0.27 - 5.99)	

Fig. 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/m^2 vs. $\geq$ 25 kg/m^2), diabetes diagnosis and smoking status. P for interaction calculated using likelihood-ratio test. Error bars show 95% confidence intervals. The dashed vertical line indicates the calculated overall odds ratio.

associated hyperglycemia is independent of the metabolic syndrome. 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]. The findings suggest 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. Although we were not able to show significant

interactions, the point estimations might have 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 pre-diagnostic 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 and thus have a low impact on pancreatic cancer mortality. Identification of additional individuals at high risk might be aided by development of risk scores based on the risk contribution of impaired fasting glucose and other risk factors for pancreatic cancer such as smoking, obesity, diabetes, heavy alcohol consumption and having a non-0 blood group [12]. 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]. Importantly, the study design and sample size does not permit any strong conclusions regarding future screening or changes in clinical practice. Larger prospective cohort studies are needed.

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. Impaired fasting glucose is an independent risk factor and should be investigated further in pancreatic cancer risk assessment including other risk factors in a larger study population.

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.

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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. 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. 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.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.05.008.

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