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ORIGINAL ARTICLE

Pattern of increasing HbA_{1c} levels in patients with diabetes mellitus before clinical detection of pancreatic cancer – a population-based nationwide case-control study

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ABSTRACT

Background. Diabetes mellitus is a risk factor for pancreatic cancer. Impaired insulin resistance might precede the clinical detection of this cancer by several years.

Methods. This was a nested case-control population-based study assessing the pattern of glycated hemoglobin (HbA_{1c}) change before clinical detection of pancreatic cancer in a population of individuals with diabetes mellitus. All patients registered in the Swedish National Diabetes Register with a prescription of an anti-diabetic drug between 2005 and 2011 were identified. For each case of pancreatic cancer, 10 controls were randomly selected, matched for age, sex, and factors related to diabetes mellitus. Multivariable conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between HbA_{1c} and pancreatic cancer.

Results. In total, 391 cases and 3910 matched controls were identified. The risk of pancreatic cancer was increased more than two-fold in individuals with the highest HbA_{1c} quartile compared with the lowest (OR 1.96, 95% CI 1.40–2.75). The risk of pancreatic cancer remained elevated when comparing the highest HbA_{1c} quartile measured within five years from the clinical detection of pancreatic cancer to the lowest HbA_{1c} quartile (p-value for trend < 0.05). No association was found between HbA_{1c} and pancreatic cancer if HbA_{1c} was measured > 5 years before the clinical detection of pancreatic cancer.

Conclusions. The pattern of increasing HbA_{1c} in patients with diabetes mellitus preceded the clinical detection of pancreatic cancer by up to five years. These findings indicate that there is a lead time of several years during which the development of pancreatic cancer might be detectable through screening in patients with diabetes mellitus.

Pancreatic cancer is one of the leading causes of cancer-related death in developed countries [1]. The cancer is often diagnosed at an advanced stage impeding surgery with curative intention [2]. Even after surgery, the prognosis remains poor with a five-year survival rate of below 20% [3].

Numerous studies have shown an association between Type 2 diabetes mellitus and pancreatic cancer [4–8]. Increased levels of markers of diabetes mellitus have been reported to be associated with pancreatic cancer in individuals without diabetes mellitus [9,10]. However, to the authors' knowledge the duration of impaired glycemic control before the clinical detection of pancreatic cancer in patients with diabetes mellitus has not been fully investigated. A complex metabolic interaction exists between the tumor and pancreatic tissue which results in insulin resistance [11]. Insulin resistance and impaired glycemic control might precede the clinical detection of pancreatic cancer in patients with diabetes mellitus [11]. To our knowledge one previous nested case-control study assessed changes in the pattern of fasting plasma glucose levels before clinical detection of pancreatic cancer [12]. In that study the level of

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fasting plasma glucose in patients with diabetes mellitus was significantly higher in cases compared with controls one year before the clinical detection of pancreatic cancer, regardless of the duration of diabetes mellitus. However, fasting plasma glucose has several disadvantages, including diurnal and intra-individual variation [13].

Glycated hemoglobin (HbA_{1c}), the most common measure of glycemic control in patients with diabetes mellitus, reflects long-term glucose concentrations. The test is not affected by the timing of the measurement or intra-individual factors [13]. We hypothesized that glycemic control, assessed as $HbA_{1c,}$ in patients with diabetes mellitus will start to deteriorate several years before the clinical detection of pancreatic cancer. Thus, a population-based nested case-control study, including patients with diabetes mellitus in Sweden, was performed to investigate the duration of impaired insulin resistance, assessed by HbA_{1c}, before the clinical detection of pancreatic cancer.

Methods

Study design

This study was a population-based nested case-control study of all patients with diabetes mellitus in Sweden with a record in the Swedish National Diabetes Register (NDR) [14] and who had a dispensed prescription of anti-diabetic drugs in the Swedish Prescribed Drug Register since July 1, 2005 [15]. The Swedish Cancer Register was used to identify all incident cases of pancreatic cancer during the follow-up between 1 July 2005 and 31 December 2011. Controls were randomly selected from the source population. The main exposure was the first recorded measurement of HbA_{1c} in the NDR since 1996. Information on potential confounders was available through linkage to other nationwide Swedish registers. Record linkage was made possible using the personal identity number that uniquely identifies each resident in Sweden [16]. The study was approved by the Ethical Review Board in Stockholm.

Sources of data

The Swedish National Diabetes Register was established in 1996 as a quality assurance register and collects information on clinically relevant data on patient visits on at least a yearly basis [14]. Informed consent has been provided by all registered patients. In 2012, the register covered almost 90% of all patients with diabetes mellitus in Sweden [17].

The Swedish Prescribed Drug Register, established in 2005 and covering the entire Swedish population, includes information on all prescribed and dispended drugs since 1 July 2005 [15]. Information on the dispensed drugs is according to the Anatomical Therapeutic Chemical (ATC) classification system.

The Swedish Cancer Register has registered information on all incident cases of cancer in Sweden since 1958. Both clinicians and pathologists are required to report new cases of cancer to the register, resulting in an overall high completeness of 96% [18]. All cancers are recorded according

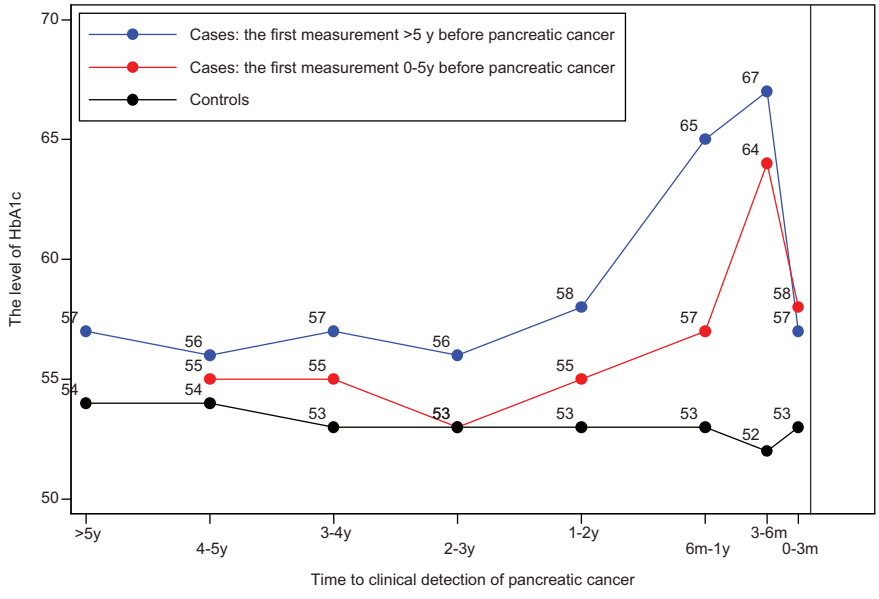

Figure 1. The level of HbA1c in relation to the clinical detection of pancreatic cancer among 391 cases and 3910 controls with diabetes.

to the International Classification of Diseases (ICD) code.

The Swedish Patient Register was established in 1964 and since 1987 has national coverage on all inpatient care and since 2001 national coverage on all outpatient specialist visits in Sweden [19]. Each record includes, among other data, information on discharge diagnosis and surgical procedures.

The Cause of Death Register has information since 1952 on all deceased Swedish residents and data on cause-specific death are 99.2% complete [20].

The National Education Register, established in 1985 by Statistics Sweden, annually updates information on the highest level of formal education attained (ranging from elementary to postgraduate level) by each Swedish resident [21].

The Register of the Total Population contains demographic information (e.g. age, sex and date of emigration) on all Swedish residents since 1968 [22].

Exclusions

Individuals with missing information on the first recorded HbA_{1c} in the NDR (n = 18 530), type of diabetes mellitus (n = 23 280), duration of diabetes mellitus (n = 35 248) and type of anti-diabetic treatment (n = 3086) were excluded from the source population. In addition, patients with secondary diabetes mellitus (n = 1515) and patients with a history of cancer diagnosis (excluding non-melanoma cancer of the skin) or cancer diagnosis (including neuroendocrine tumors of the pancreas) apart from pancreatic cancer during the follow-up (n = 35 554) were also excluded. Such exclusions resulted in a source population of 243 221 patients with diabetes mellitus registered in the NDR.

Identification of cases and controls

Cases had an incident diagnosis of pancreatic cancer and the date of cancer diagnosis was later than the first record in the NDR. Controls were cancer-free individuals with diabetes mellitus who did not develop cancer (excluding non-melanoma cancer of the skin) during the study follow-up. Person-time was calculated for all individuals in the source population. Censoring was made at date of death or emigration, whichever occurred first. For each case, 10 controls were randomly sampled using density-based sampling [23]. The probability of becoming a control was proportional to the time at risk during the study period. Controls were frequency matched for sex, age (categorized in quartiles: <60, 60–66, 67–72, ≥ 73 years), duration of diabetes mellitus (categorized in quartiles: ≤ 1, 1–5, 6–11, >11 years), type of diabetes mellitus (Types 1 and 2), and the year of the first record in the NDR [1996–2003 (quartiles 1 and 2), 2004–2006 (quartile 3), >2006 (quartile 4)].

Exposure was considered in relation to an index date assigned to each case and control. For cases, the index date was set as the diagnosis date of pancreatic cancer. For controls, the index date was a randomly assigned date during the study period (2005–2011).

HbA_{1c}

The main exposure was the first recorded measurement of HbA_{1c} in the NDR. The first recorded measurement was used to minimize potential bias introduced by multiple measurements. The HbA_{1c} analyses were quality assured nationwide by regular calibration with the HPLC Mono-S method. The HbA_{1c} values were converted to the IFCC standard using the formula: HbA_{1c} (IFCC) = 10.11 × (Mono-S)–8.94, and to DCCT by using the formula: HbA_{1c} (DCCT) = 0.9236 × HbA_{1c} (Mono-S) + 1.345; R2 = 0.998 [24]. The HbA_{1c} levels were categorized in quartiles based on the measured levels in the control population [quartile 1: 27–45 mmol/mol (IFCC), 4.6–6.3% (DCCT); quartile 2: 46–51 mmol/mol (IFCC), 4.6–6.8% (DCCT); quartile 3: 52–60 mmol/mol (IFCC), 6.9–7.6% (DCCT); and quartile 4: 61–145 mmol/mol (IFCC), 7.7–15.4% (DCCT)].

Pancreatic cancer

Using the Swedish Cancer Register, patients with a histologically verified diagnosis of pancreatic cancer (ICD-10 code C250, C251, C252, C257, C258, and C259) were identified. No patient with endocrine pancreatic cancer was included.

Confounders

Educational level (categorized as <9 years, 9 years, 10–12 years, >12 years, unknown or missing) was used to estimate socioeconomic position. The Swedish Patient Register was used to identify patients with complicated diabetes mellitus, including a history of myocardial infarction, heart failure, stroke or peripheral vascular disease, renal insufficiency, polyneuropathy or retinopathy before the first record in the NDR. In addition, patients with macro-albuminuria or polyneuropathy in the first NDR record were classified as having complicated diabetes mellitus. Information on smoking and body mass index (BMI) was retrieved from the NDR. BMI was measured using the formula weight (kg)/height^2 (cm). BMI was categorized into normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥ 30 kg/m^2). Furthermore, previous hospitalization for alcohol

abuse (excessive alcohol consumption or alcohol-related disease) and pancreatitis were also identified using the Swedish Patient Register.

Statistical analyses

Conditional logistic regression was used to calculate odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the association between the level of HbA_{1c} and pancreatic cancer. Two statistical models were constructed: Model 1 was the crude model without any adjustment for confounders. Model 2 was adjusted for educational level, alcohol abuse, complicated diabetes mellitus, smoking and body mass index. No adjustment was applied for the type of anti-diabetic treatment because the choice of treatment is a consequence of glycemic control, which is the exposure in the current study.

The full model was irrespective of the latency between the first record in the NDR and the diagnosis of pancreatic cancer. The potential interaction between the timing of HbA_{1c} measurement with regard to clinical detection of pancreatic cancer (≤ 6 months, 6 months–1 year, >1 year–2 years, >2 years–5 years, >5 years) was examined by testing the statistical significance of the interaction term with the Wald test. The statistical analyses were performed using Stata v.11.2 (StataCorp).

Results

There were 391 incident cases of pancreatic cancer between 1 July 2005 and 31 December 2011 and 3910 matched controls using density-based sampling. Frequency-matching resulted in a similar distribution of sex, age, duration of diabetes mellitus, type of diabetes mellitus and year of the first record in the NDR between cases and controls (Table I). The median age was 67 years, 56% were men and the median duration of diabetes mellitus at the time of the first record in the NDR was three years. Distribution of education level was similar, except the controls were more likely to have unknown or missing information on education level. No statistically significant differences were observed in complicated diabetes mellitus, history of alcohol abuse or previous pancreatitis between cases and controls. However, smoking was more common in the cases (19%) than in the controls (12%). There were no substantial differences in the use of anti-diabetic treatment between cases and controls and both groups were more likely to use oral anti-diabetic treatment (46% of cases and 46% of controls).

The longitudinal changes in the level of HbA1c among cases and controls were graphically shown in relation to the timing of HbA1c measurement before the clinical detection of pancreatic cancer (Figure 1). In cases, the HbA1c level increased 1–2 years prior to the clinical detection of pancreatic cancer and reached the highest levels 3–6 months before the diagnosis of cancer. This pattern was similar whether the first record of HbA1c in NDR was measured >5 years or ≤ 5 years before the clinical detection of pancreatic cancer. For controls the level of HbA1c was stable and showed little change irrespective of the timing of measurement Comparing the highest HbA_{1c} quartile to the lowest in the crude model, the risk of pancreatic cancer increased by almost two-fold (OR 1.95; 95% CI 1.40–2.73) (Table II). The corresponding association increased by 64% when comparing quartile 3 to the lowest quartile (OR 1.64; 95% CI 1.17–2.29). Adjustment for potential confounders changed the results only marginally. A statistically significant interaction was noted between the timing of the HbA_{1c} measurement in the NDR and the clinical detection of pancreatic cancer (p-value for interaction <0.01). In stratified analyses an increase in the risk of pancreatic cancer persisted when comparing the highest to the lowest quartile of HbA_{1c} within the first five years from the clinical detection of pancreatic cancer (p-value for trend <0.05). This association increased almost five-fold within six months from clinical detection of pancreatic cancer (OR 4.73; 95% CI 1.83–12.21) (Table III). This association declined but was increased up to five years before the clinical detection of pancreatic cancer (OR 2.70; 95% CI 0.99–7.36 for HbA_{1c} measured >6 months–1 year before the clinical detection of pancreatic cancer; OR 2.51; 95% CI 1.17–5.40 for HbA_{1c} measured >1–2 years before the clinical detection of pancreatic cancer; and OR 1.77; 95% CI 0.99–5.40 for HbA_{1c} measured >2–5 years before the clinical detection of pancreatic cancer). No clear association was found between the timing of HbA_{1c} when comparing the second and third quartile of HbA_{1c} to the lowest quartile. HbA_{1c} measured >5 years before the clinical detection of pancreatic cancer was not associated with this cancer.

Discussion

In this population-based study on patients with diabetes mellitus the pattern of increased HbA_{1c} levels was present up to five years before clinical detection of pancreatic cancer.

Strengths of this study include the nationwide population-based design, the prospective nature of the exposure data assessment and the complete follow-up of all patients using linkage to high-quality national registers on cancer, death and emigration. The information on the level of HbA_{1c} was available for over 14 years, making it possible to assess the

Table I. Baseline characteristics of 391 pancreatic cancer patients with diabetes mellitus and 3910 matched controls.

	Patients N = 391	Controls N = 3910	p-Value
Age, years (median, range)	67 (35–93)	67 (20–102)	[a]
Age, years			[a]
≤65	68 (17)	680 (17)	
60–66	120 (31)	1200 (31)	
67–72	90 (23)	900 (23)	
≥73	113 (29)	1130 (29)	
Sex			[a]
Men	220 (56)	2200 (56)	
Women	171 (44)	1710 (44)	
Educational level			0.04
<9 years	105 (27)	1053 (27)	
9 years	31 (8)	265 (7)	
10–12 years	145 (37)	1231 (31)	
>12 years	43 (11)	455 (12)	
Unknown or missing	67 (17)	906 (23)	
Duration of diabetes, years (median, range)	3 (0–56)	3 (0–57)	[a]
Duration of diabetes, years			[a]
≤1	149 (38)	1490 (38)	
>1–5	98 (25)	980 (25)	
>5–11	82 (21)	820 (21)	
>11	62 (16)	620 (16)	
Year of registration			[a]
1996–2003	96 (25)	960 (25)	
2004–2006	157 (40)	1570 (40)	
2006–2010	138 (35)	1380 (35)	
Type of diabetes			[a]
Type 1	8 (2)	80 (2)	
Type 2	383 (98)	3830 (98)	
Type of anti-diabetic treatment			0.02
No medication	1104 (28)	84 (21)	
Oral anti-diabetic drugs	1779 (46)	178 (46)	
Insulin	582 (15)	71 (18)	
Oral anti-diabetic drugs and insulin	445 (11)	58 (15)	
Complicated diabetes	131 (34)	1286 (33)	0.81
Smokers	73 (19)	453 (12)	<0.01
Previous pancreatitis	13 (3)	80 (2)	0.10
Alcohol abuse	16 (4)	100 (3)	0.07
Body mass index (kg/m^2)			<0.01
18.5–24.9	80 (20)	630 (16)	
25–29.9	159 (41)	1514 (39)	
30–max	111 (29)	1474 (38)	
Missing	41 (10)	292 (7)	

[a]Matching variables.

Table II. The risk of pancreatic cancer in relation to the quartiles of plasma HbA_{1c} expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

	Quartiles of HbA_{1c}				
	1	2	3	4	p-Value for trend
HbA_{1c}, median (range)					
IFCC measures	42 (27–45)	48 (46–51)	55 (52–60)	71 (61–145)	
DCCT measures	6.0 (4.6–6.3)	6.5 (6.4–6.8)	7.2 (6.9–7.6)	8.6 (7.7–15.5)	
Cases/Controls, n	58/855	88/953	112/1038	133/1064	
Crude model	Reference	1.37 (0.97–1.94)	1.64 (1.17–2.29)**	1.95 (1.40–2.73)**	<0.01
Adjusted model[a]		1.37 (0.97–1.94)	1.64 (1.17–2.30)**	1.96 (1.40–2.75)**	<0.01

[a]The model was adjusted for education, smoking, body mass index, alcohol abuse, complicated diabetes disease and previous pancreatitis. *$p < 0.05$; **$p < 0.01$.

Table III. The risk of pancreatic cancer in relation to the quartiles of plasma HbA_{1c} and time between time of measurement and diagnosis of pancreatic cancer. The estimates were expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Quartiles of HbA_{1c}	Time between plasma sample and diagnosis of pancreatic cancer				
	0–6 months	>6 months–1 year	>1–2 years	>2–5 years	>5 years
1	Reference	Reference	Reference	Reference	Reference
Cases/controls, n	6/138	6/98	11/175	21/317	14/127
2	2.18 (0.80–5.98)	0.87 (0.27–2.80)	1.37 (0.61–3.11)	1.52 (0.86–2.70)	0.91 (0.41–2.02)
Cases/controls, n	14/152	7/124	16/182	36/359	15/136
3	1.46 (0.51–4.23)	2.24 (0.82–6.13)	1.56 (0.69–3.52)	1.86 (1.07–3.25)*	0.98 (0.47–2.04)
Cases/controls, n	10/140	15/117	17/175	47/397	23/209
4	4.73 (1.83–12.21)**	2.70 (0.99–7.36)	2.51 (1.17–5.40)*	1.77 (0.99–3.19)	0.69 (0.32–1.48)
Cases/controls, n	27/140	16/101	25/158	39/355	26/307
p-Value for trend	<0.01	<0.05	<0.05	<0.05	0.35

[a]The model was adjusted for education, smoking, body mass index, alcohol abuse, complicated diabetes disease and previous pancreatitis. *$p < 0.05$; **$p < 0.01$.

pattern of HbA_{1c} change long before clinical detection of pancreatic cancer. There are some methodological considerations. It is reasonable to assume that patients with sub-clinical pancreatic cancer, with impaired cancer-related glycemic control, might undergo more frequent clinical examination and blood testing. However, in this study only the first measurement of HbA_{1c} was included minimizing the role such bias on the observed associations. The first record in the NDR was not necessarily the time of the diagnosis of diabetes mellitus. Therefore, this study was not able to fully distinguish between new-onset and long-lasting diabetes mellitus. However, the median duration of diabetes mellitus was three years and the observed associations were present up to five years before the clinical detection of pancreatic cancer. There might be residual confounding by alcohol abuse, body mass index or smoking. However, such residual confounding would not explain the observed pattern of HbA_{1c} change before clinical detection of pancreatic cancer.

Several studies have shown an association between Type 2 diabetes mellitus and pancreatic cancer [4–8], and previous studies have investigated the role of markers for diabetes mellitus in a population without diabetes as risk factors for pancreatic cancer [9,10]. However, to the best of our knowledge the duration of impaired glycemic control before the clinical detection of pancreatic cancer in individuals with diagnosed diabetes mellitus has not been fully investigated. One nested case-control study assessed the pattern of fasting plasma glucose change and pancreatic cancer [12]. In patients with new-onset diabetes mellitus, i.e. diabetes detected <2 years before diagnosis of pancreatic cancer, the cases had statistically significantly higher median levels of fasting plasma glucose than the controls one year before the clinical detection of pancreatic cancer. The same finding was observed in patients with long-lasting diabetes mellitus. In the current study there was a pattern of increasing HbA_{1c} levels observed as early as five years before the clinical detection of pancreatic cancer.

Several tumor-related mechanisms have been proposed to affect pancreatic function in pancreatic cancer patients [11]. The tumor-related destruction of the pancreatic tissue could result in deteriorated pancreatic function. However, it is unlikely that the destruction of the pancreatic tissue could explain deteriorated levels of HbA_{1c} several years before clinical detection of pancreatic cancer. Likewise, cancer-related cachexia is a late phenomenon. The complex metabolic interaction between pancreatic cancer and the pancreas resulting in insulin resistance might explain the early changes in the level of HbA_{1c} many years before clinical detection of pancreatic cancer.

Pancreatic cancer is often diagnosed at a late stage without the possibility of curative surgery [2]. In many patients tumor recurrence occurs after surgery resulting in poor survival rates [3]. Therefore, the prerequisite for curability is the early detection of pancreatic cancer at a pre-invasive stage [25]. Currently, no reliable or efficient biomarkers are available for early detection of pancreatic cancer [26]. It seems that the transition from a resectable to an unresectable pancreatic cancer occurs approximately six months before clinical detection of pancreatic cancer [25]. Our findings indicate a lead time of several years during which pancreatic cancer might be detectable through screening years before diagnosis. Thus, the long latency between the changes in HbA_{1c} and the clinical detection of pancreatic cancer in patients with diabetes mellitus would provide a window of opportunity to identify patients with asymptomatic and potentially curable pancreatic cancer. Whether HbA_{1c} or other biomarkers could be used for such screening remains to be clarified.

In conclusion, we observed that increased levels of HbA_{1c} in patients with diabetes mellitus precede

the clinical detection of pancreatic cancer by up to five years. Such a lead time would provide a unique opportunity to detect pre-clinical and potentially curable pancreatic cancer.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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