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CLINICAL—PANCREAS

Mortality, Cancer, and Comorbidities Associated With Chronic Pancreatitis: A Danish Nationwide Matched-Cohort Study

Ulrich Christian Bang,[1] Thomas Benfield,[2,3] Lars Hyldstrup,[1,3] Flemming Bendtsen,[3,4] and Jens–Erik Beck Jensen[1,3]

[1]Department of Endocrinology, [2]Department of Infectious Diseases, [4]Department of Gastroenterology, Copenhagen University Hospital of Hvidovre, Hvidovre, Denmark; [3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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BACKGROUND & AIMS: We aimed to assess the risk of death, cancer, and comorbidities among patients with alcoholic and nonalcoholic chronic pancreatitis (CP). **METHODS:** We performed a nationwide retrospective cohort study, collecting data from Danish registries from 1995 through 2010. We evaluated the prevalences and incidences of death, cancers, and comorbidities among subjects with CP (cases) compared with age- and sex-matched individuals (controls). In total, 11,972 cases (71,814 person-years) and 119,720 controls (917,436 person-years) were included in the analysis. Hazard ratios (HR) were estimated by Cox proportional hazards regression. **RESULTS:** Forty-six percent of the cases died during the follow-up period, compared with 13.0% of controls (mean age, 63.7 vs 72.1 y; $P < .0001$), corresponding to a HR of 5.0 for CP (95% confidence interval [CI], 4.8–5.2). Cancer was a frequent cause of death among cases (10.2%) and controls (3.3%). Cancer (particularly pancreatic cancer) was a frequent cause of death among cases; the HR was 6.9 (95% CI, 7.5–11.8). Alcoholic CP did not produce a higher risk for cancer or death than nonalcoholic CP. Cerebrovascular disease (HR, 1.3; 95% CI, 1.2–1.4), chronic pulmonary disease (HR, 1.9; 95% CI, 1.8–2.1), ulcer disease (HR, 3.6; 95% CI, 3.3–3.9), diabetes (HR, 5.2; 95% CI, 5.0–5.6), and chronic renal disease (HR, 1.7; 95% CI, 1.5–1.9) occurred more frequently among patients with CP, but myocardial infarction did not (HR, 0.9; 95% CI, 0.8–1.0). **CONCLUSIONS:** Based on a Danish nationwide cohort study, individuals with CP are at higher risk for death from cancer (particularly pancreatic cancer) and have a higher incidence of comorbidities than people without CP.

Keywords: Pancreas; Inflammation; Malignancy; Epidemiology.

Chronic pancreatitis (CP) is a disease with a variety of etiologies that throughout the Western world is triggered most often by alcohol.[1] Fibrosis of the pancreas often is accompanied by fat malabsorption, secondary diabetes, and an increased risk of pancreatic cancer.[2,3] Earlier studies on mortality resulting from CP have documented an increased risk of death but have been based on cohorts with 82–249 patients, which have limited the statistical precision.[1,4–6] In general, previous studies have included patients from tertiary referral hospitals and the aims of this study were to evaluate the causes of death and types of cancer in patients with CP in a nationwide population-based cohort. Furthermore, we investigated the risk of other comorbidities.

Methods

Study Population

We performed a matched retrospective cohort study. Patients diagnosed with CP (cases) between 1995 and 2010 were identified from the Danish National Patient Register, which contains discharge diagnoses from all inpatient and outpatient contacts.[7] We used the International Classification of Disease 10th edition codes K86.0 (alcoholic CP) and K86.1 (nonalcoholic CP). Each case was compared with 10 age- and sex-matched controls without CP, who were retrieved from the Danish Civil Registration System.[8] CP cases could not enter the control group.

Outcomes

Our primary outcome was risk of death and we retrieved all mortality diagnoses from the Danish Register of Causes of Death.[9] The following International Classification of Disease 10th edition codes were used for mortality diagnoses: Cxx: malignancies, Kxx: alimentary tract, Ixx: circulatory system, Jxx: respiratory system, Exx: endocrine, Fxx: psychiatric, A0/A2–A9/Bxx: infectious, X6/X7/X81–X84/Y870: suicide, and V/X1–X5/Y1–Y7/Y80–Y86/Y872/Y8: accidents.

Furthermore, we retrieved all discharge diagnoses assigned to the participants throughout the time of follow-up evaluation. We evaluated the incidences of the following gastrointestinal cancer types: C15: esophagus, C16: gastric, C17: small intestine, C18: colon, C22: hepatic, C25: pancreatic, together with C34: lung, and C43: melanoma. We further distinguished between cancer of the pancreatic head (C250), body (C251), tail (C252), and ducts of the pancreas (C253). When studying the time-dependent relationship between the diagnosis of CP and pancreatic cancer, we only wanted to include newly diagnosed cases of CP and therefore omitted the prevalent cases of CP on

Abbreviations used in this paper: **AMI, acute myocardial infarction; CI, confidence interval; CP, chronic pancreatitis; CPD, chronic pulmonary disease; HR, hazard ratio; IR, incidence rate; PY, person-year.**

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January 1, 1997. We further disregarded the cases of pancreatic cancer that occurred within 1 year after the diagnosis of CP to account for pancreatic cancers that were present at the time of CP diagnosis.

We evaluated the incidence of the following other comorbidities: I21–I23: acute myocardial infarction (AMI), I60–I69/G45/G46: cerebrovascular disease, J40–J47/J60–J67/J684/J701/J703/J841/J920/J961/J982/J983: chronic pulmonary disease (CPD), K221/K25–K28: ulcer disease, E100/E101/E109/E110/E111/E119: diabetes, and I12/I13/N00–N05/N07/N11/N14/N17–N19/Q61: renal disease.

Covariates

We retrieved information on date of birth, sex, and socioeconomic status from the Danish Civil Registration System, which is updated daily and tracks changes in demographic characteristics of Danish residents.[8] In the analysis of mortality and malignancy, we included the Charlson comorbidity index as a covariate, which was based on discharge diagnoses registered for each participant (Supplementary Table 1).[10] In the analysis of malignancy, the Charlson index was based solely on morbidity diagnoses reported before the diagnosis of cancer.

Statistics

Baseline characteristics were presented as means with standard deviation (SD) or medians with interquartile range (Q1–Q3) where appropriate. Cohort entry was the time of first CP diagnosis within the years 1995–2010 and each control was assigned a cohort entry date identical to the matching case's date of CP diagnosis. Risk time was expressed in person-years (PYs) and was defined as the time from cohort entry until occurrence of an event, death, or end of follow-up evaluation (December 31, 2010). The results were reported in prevalences, incidence rates (IRs) in numbers per 1000 PYs, or hazard ratio (HR) with 95% confidence interval (CI). We used univariate and multivariate Cox proportional hazard models to assess the HR. The risk time was split into periods of 4 years and included as a covariate to account for nonproportional hazards throughout the follow-up period (extended Cox regression model). Persons with missing data were excluded from the analyses (0.03%). All analyses were performed using SAS 9.2 (SAS Institute, Inc, Cary, NC). The study was approved by the Danish Health and Medicines Authority and followed the regulations set up by the Danish Data Protection Agency.

Results

In total, 11,972 persons (33.5% women) with CP were identified and matched with 119,720 controls with a median age of 54 years (Q1–Q3, 45–64 y). Alcohol as the etiology to CP was reported for 6306 (52.7%) of the CP cases. Baseline values are presented in Table 1.

Mortality

All mortality diagnoses among the cases and controls are presented in Table 2. Of the 11,972 persons with CP, 5560 (46.4%) died during the follow-up period compared with 15,528 (13.0%) persons in the control group. Age at time of death was significantly lower in the CP group (63.7 y) compared with the control group (72.1 y; $P < .0001$). Mortality rates were 77.4 (95% CI, 75.4–79.5) in the CP cohort and 16.9 (95% CI, 16.7–17.2) per 1000 PYs in the control cohort, yielding an adjusted HR of 5.0 (95% CI, 4.8–5.2). Mortality rates increased considerably with age in both cases and controls (Supplementary Figure 1), but the adjusted relative risks of death were significantly higher for the younger CP cases than among older patients ($P < .0001$) (Figure 1). The excess mortality risk in CP patients was comparable between alcoholic and nonalcoholic CP (Cox regression analysis, $P = .7$).

The most frequently reported mortality diagnoses among the patients with CP were diseases of the alimentary tract (10.6%)—mainly resulting from CP and alcoholic cirrhosis—followed by cancer (10.2%) and circulatory system diseases (5.5%). In comparison, only 0.4% of the controls

Table 1. Baseline Characteristics of Cases and Controls

	CP	Controls
N	11,972	119,720
Women, %	33.5	33.5
Age at entry, mean (SD), *y*	54.5 (14)	54.5 (14)
Deceased, n (%)	5560 (46)	15,528 (13)
Age at death, mean (SD), *y*	63.8 (13)	73.1 (12)
Socioeconomic status, %		
Working	28	58
Unemployed	14	7
Retired	58	35
Charlson index, median (Q1–Q3)	2 (1–5)	0 (0–1)
0	22%	62%
1–2	34%	25%
>2	44%	13%

Table 2. Causes of Mortality Associated With CP Compared With Controls

	CP	Controls	HR[a]	95% CI
Number	11,972	119,720		
Person-years	71,814	917,436		
	% of total	% of total		
Death from all causes	46.4	13.0	5.0	4.8–5.2
Malignancies	10.2	3.3	1.4	1.3–1.5
Alimentary tract	10.6	0.4	26.1	23.1–29.4
Circulatory system	5.5	3.2	1.9	1.7–2.1
Respiratory system	2.8	1.0	3.3	2.8–3.8
Endocrine disorder	2.2	0.4	4.2	3.6–4.9
Psychiatric disorder	2.1	0.4	6.3	5.4–7.5
Infectious disease	0.6	0.1	4.4	3.2–6.0
Suicide	0.4	0.1	3.5	2.6–4.7
Accident	1.5	0.3	4.1	3.5–5.0
Missing diagnosis	7.8	2.7	N/A	N/A
Other diagnosis	2.1	1.1	1.3	1.1–1.4

HR, hazard ratio.
[a]Adjusted for Charlson index and socioeconomic status.