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Risk Factors for Pancreatitis in Older Women: The Iowa Women's Health Study

Anna E. Prizment, PhD, MPH,

Division of Epidemiology & Community Health, School of Public Health, Masonic Cancer Center, University of Minnesota; Minneapolis, MN 55455, USA

Eric H. Jensen, MD,

Division of Surgical Oncology, University of Minnesota Medical School, Minneapolis, MN 55455, USA

Anne M Hopper, MPH,

Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota 55455, USA

Beth A. Virnig, PhD, and

Division of Health Policy and Management, School of Public Health, Masonic Cancer Center, University of Minnesota; Minneapolis MN 55455, USA

Kristin E. Anderson, PhD, MPH

Division of Epidemiology & Community Health, School of Public Health, Masonic Cancer Center, University of Minnesota; Minneapolis, MN 55455, USA

Anna E. Prizment: prizm001@umn.edu; Eric H. Jensen: jense893@umn.edu; Anne M Hopper: hoppe147@umn.edu; Beth A. Virnig: virni001@umn.edu; Kristin E. Anderson: ander116@umn.edu

Abstract

Purpose—Pancreatitis – an inflammation of pancreas – is a severe and costly disease. While many risk factors for pancreatitis are known, many cases, especially in elderly, are of unknown etiology.

Methods—Risk factors for acute (AP) and chronic pancreatitis (CP) were assessed in a prospective cohort (n=36,436 women, aged 65 years). Exposures were self-reported at baseline. Pancreatitis was ascertained by linkage to Medicare claims (1986–2004) categorized by a physician as: “AP”, 1 AP episode (n=511); or “CP”, 2+ AP or 1+ CP episodes (n=149).

Results—Multivariable odds ratios (OR) and 95% CI for AP and CP were calculated using multinomial logistic regression. Alcohol use was not associated with AP or CP. Heavy smoking (40+ versus 0 pack-years) was associated with a 2-fold increased OR for CP. For BMI 30 versus <25 kg/m², the ORs were 1.35 (1.07–1.70) for AP (p-trend=0.009) and 0.59 (0.37–0.94) for CP

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Correspondence author: Anna E Prizment, Division of Epidemiology & Community Health, School of Public Health, University of Minnesota; 1300 S. 2nd Street Suite 300, Minneapolis, MN 55454; phone 612-626-0250; prizm001@umn.edu.

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(p-trend=0.01). ORs for AP and CP were increased for HRT use, heart disease, and hypertension. There were positive significant associations between protein and total fat intake for CP and AP.

Conclusions—We identified factors associated with AP and CP that may be specific to older women.

Keywords

Pancreatitis; elderly; cohort; Medicare

Introduction

Pancreatitis, an inflammatory condition leading to pancreatic tissue damage, causes substantial morbidity and mortality^{1,2}. Pancreatitis develops when digestive enzymes produced by the exocrine pancreas become activated in the pancreas instead of the small intestine, causing inflammation and tissue damage in the pancreas².

Pancreatitis can be acute (AP), with sudden onset and usually resolving within several of days, or chronic (CP), occurring over many years. Annually, approximately 210,000 people with AP are admitted to the hospital in the United States; about 5% of all AP patients die^{2,3}. CP occurs when pancreatic inflammation does not completely resolve and is stable or worsens over time, causing permanent tissue damage². Diagnosing pancreatitis (acute or chronic) may be difficult; it requires that two out of three criteria (clinical presentation with abdominal pain, elevated amylase or lipase, or radiographic evidence) be met³. Symptoms of an exacerbation of CP are often the same as AP⁴.

Established causes of pancreatitis include gallstones, heavy alcohol use and hereditary disorders; potential risk factors include use of certain medications, smoking, diet rich in fat and proteins, metabolic factors (e.g. hypertriglyceridemia, hypercalcemia)^{1,2,4–6}. Yet, approximately 20% of AP and CP cases are considered idiopathic with no obvious risk factors^{7–9}. Because there is no specific treatment for pancreatitis, understanding the etiology of this disease is critical for developing preventive and therapeutic approaches. In this study we characterized risk factors for AP and CP among 36,436 women ages 65 years and older in the prospective cohort – Iowa Women's Health Study (IWHS).

Materials and Methods

The IWHS has been described in detail^{10,11}. Briefly, 41,836 post-menopausal women aged 55–69 years were recruited at baseline (1986). Subjects completed a baseline and five follow-up questionnaires addressing demographics, anthropometrics, lifestyle, medical history, hormone replacement therapy (HRT), diet, physical activity and other factors¹⁰. Annual linkage to the Iowa SEER registry provided cancer incidence, while linkage to the National Death Index provided mortality¹⁰. The University of Minnesota Institutional Review Board approved this study and all participants gave consent.

The data for IWHS participants 65+ years old were linked to Centers for Medicare Services claims (1986–2004) by social security number, first and last name, and date of birth¹¹, since US residents become eligible for Medicare at 65 years. Linkage to participants 65+ years old

was successful for 99% of the cohort members alive at 65¹². Pancreatitis cases were ascertained through Medicare hospital, carrier and outpatient claims¹³. Women with 1 hospitalizations or 2 claims from the outpatient or carrier files with an ICD-9 diagnosis code 577.0 (AP) or 577.1 (CP) were selected and reviewed by a physician. The physician categorized patients as definite, probable or uncertain pancreatitis. We were conservative and excluded “uncertain” cases, i.e. cases with insufficient data to confirm pancreatitis. Pancreatitis cases were categorized as AP, if women had one acute pancreatitis episode and CP, if women had 2 episodes of acute pancreatitis that were at least 6 weeks apart or one episode of chronic pancreatitis. Also, women were excluded if their first pancreatitis episode was within ± 6 months of SEER-identified gastrointestinal cancer.

We used multinomial logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI) for AP and CP in relation to BMI, smoking (status and pack-years), heart disease or attack, diabetes, hypertension, hormone replacement therapy (HRT) use, alcohol use, dietary factors (all assessed at 1986 baseline) and aspirin use (assessed at 1992).

All models were adjusted for age and the time of Medicare enrollment. The models for BMI and smoking were adjusted for each other. All other models were adjusted for age, Medicare enrollment, BMI, and smoking status and pack-years. Additionally, analyses of dietary factors were adjusted for total energy intake. Odds ratios and p-values for trend were computed using SAS 9.3. Tests for trend were conducted by including a categorical variable as an ordinal continuous variable in the model.

Results

During follow up through 2004, 511 AP and 149 CP eligible cases were identified among 36,436 women older than 65 years (mean age $\pm$ SD at enrollment was 65.8 ± 1.6 years; 99.2% white). The mean ages of the AP and CP diagnosis were 75.3 ± 5.5 and 73.3 ± 5.5 years, respectively. At baseline, 23% of the cohort was obese, 14% were current smokers, and 43% consumed alcohol (Table 1).

Cigarette smoking was associated with CP: for 40+ versus 0 pack-years with an OR=2.03 (95%CI: 1.23–3.34) (p-trend=0.02). BMI was positively associated with AP and inversely associated with CP: for 30 versus <25 kg/m², the ORs were 1.35 (95%CI: 1.07–1.70) (p-trend=0.009) and 0.59 (95%CI: 0.37–0.94) (p-trend=0.01), respectively (Table 2). ORs for AP and CP were increased for HRT use (18% for AP and 97% for CP), heart disease (43% for AP and 94% for CP), and hypertension (37% for AP and 47% for CP). We found an association between aspirin use 6 times per week and AP: OR=1.44 (95%CI: 1.08–1.91) versus no aspirin use (p-trend=0.04). We did not observe associations of alcohol or self-reported diabetes with either AP or CP (Table 2).

In the analysis of dietary factors and AP, we found an increased risk associated with total and saturated fat intake. For CP, we observed marginally statistically significant trends for saturated fat and protein intakes.

Discussion

In our study of women 65+ years, we confirmed several known risk factors for pancreatitis. Consistent with previous studies^{1,14}, heavy cigarette smoking (40+ versus 0 pack-years) was associated with a 2-fold increased risk for CP, while BMI was associated with a moderately increased risk for AP, as shown in two meta-analyses^{15,16}. The potential mechanisms for a BMI–AP association may be through inflammation accompanying obesity and/or gallstone disease, which is a known risk factor for pancreatitis¹. As gallstone disease is common in obese people, it may mediate the obesity–AP association¹⁷. Further, in our study, BMI was inversely associated with CP, which is most likely explained by reverse causality: 75% of CP patients lose weight due to difficulties in digesting foods².

Interestingly, diabetes and alcohol use, two established risk factors, were not associated with either AP or CP in our study. Alcohol is commonly associated with pancreatitis in men^{1–3,18}; however, the association for women has been less consistent, suggesting different pancreatitis etiology for men and women. One study found that the association between alcohol consumption and CP in men, OR=4.56 (95%CI: 2.22–9.36) was much stronger than in women OR=1.95 (95%CI: 0.90–4.24)¹⁹. Another study reported a positive association between alcohol use and pancreatitis in men but no association in women, which supports the null findings observed in our study²⁰. Also, it was shown that the CP risk associated with alcohol increased at a threshold of 5+ drinks/day in a case-control study¹⁹ and 4+ drinks/day in a meta-analysis of published data²¹. Thus, a lack of alcohol–pancreatitis association in our study may be explained by low alcohol consumption: 7% of IWHs women had 1+ drink per day, and only 1% of women consumed 3+ drinks/day.

In our study, self-reported diabetes was not associated with pancreatitis, although most of the studies have reported associations of diabetes with AP^{1,22} and CP^{9,23}. The lack of the association in our study might reflect misclassification of self-reported diabetes²⁴. Under-diagnosis is known in self-reporting diabetes²⁴. However, in the IWHs, a validation study of 44 self-reported diabetes cases found that only 28 (63.6%) diabetes cases were confirmed by a physician, suggesting an over-reporting²⁵. Therefore, either over- or under-diagnosis²⁴ could result in bias towards the null. Aside from these biases, it is possible that indeed no association exists between diabetes and pancreatitis among elderly IWHs women.

We also observed that in multivariable models, hypertension, heart disease and saturated fat intake were associated with AP and CP; total fat intake was associated with AP; and protein intake was associated with CP. There is little previous research on these factors in relation to pancreatitis. An increased risk of CP associated with fat and protein intake was observed in some earlier^{5,6}, but not all studies^{26–28}, although a biological mechanism has been proposed for the fat–pancreatitis association. Dietary fat has been shown to stimulate pancreatic secretion²⁹ and long-term fat diet caused pancreatic injury in rats^{30,31}. In addition, several studies found that elevated triglyceride levels led to the production of free fatty acids toxic to the pancreas³² and may cause AP^{33–35}. In one study, 12%–38% of patients had high triglyceride levels at the time they presented with AP³⁵. Finally, studies reported an important role of oxidative stress in CP³⁶, which could partially explain associations with fat intake, triglycerides, and heart disease. It would be useful to determine whether or not fat,

protein intake, high triglycerides are causally related to pancreatitis; if causal, pancreatitis might be prevented through a change in diet and/or use of lipid-lowering agents.

Drug-induced pancreatitis accounts for approximately 1–2% of acute pancreatitis cases³⁷. Angiotensin-converting enzyme (ACE) inhibitors are a category of drug used to treat hypertension. Case reports have shown an increase in risk of developing acute pancreatitis associated with ACE inhibitor use due to the obstruction of the pancreatic duct by localized angioedema^{37,38}. The associations between hypertension and both AP and CP found in our study may reflect an association between the use of ACE inhibitors for hypertension treatment and pancreatitis, but we did not have access to treatment information, so further investigation of these relationships is warranted.

Finally, we observed an association of HRT use with both AP and CP, which is in agreement with other studies^{39,40}. A prospective study of over 31,000 Swedish women reported that women who had ever used HRT had a 57% greater risk of developing AP than never users; the risk did not differ significantly between present and former use³⁹. Given that a substantial proportion of women in the U.S. report HRT use (38.5% in the IWHs), it is important to further evaluate this association.

Our study's major strength was the use of a large, population-based prospective cohort with close to complete follow-up (loss to follow-up of 0.5%¹⁰) and detailed information about various risk factors. Further, using Medicare to identify pancreatitis, instead of relying on self-report, removed possible recall or non-response bias. Our study also had limitations. We use diagnosis codes from Medicare administrative data. While algorithms to identify outcomes from such data have been successful for large number of different diseases, including type 2 diabetes and hypertension^{41–43}, it is not possible to distinguish between an actual diagnosis and a rule-out diagnosis or to completely dismiss simple miscoding. This is especially true for pancreatitis because its diagnosis is clinically challenging; it requires a complex clinical algorithm⁴ and therefore patients are at high risk for misdiagnosis which would carry-over into claims. Previous studies that used administrative data to ascertain gastrointestinal diseases indicated difficulties in creating algorithms for pancreatitis and other diseases^{43,44}. For instance, one study that initially identified over 9,000 potential cases of gastrointestinal diseases via computer-based algorithms was able to verify only 152 cases after manual review of insurance claims and medical records⁴³. Hence, we used the combination of an algorithm and physician coding to classify pancreatitis.

Temporality is another limitation in our study, especially for assessing whether cases represent AP or CP. A majority of CP cases first present before age 65^{1,2,45}. The minimum age of pancreatitis ascertainment for our cohort was 65 years old. It is reasonable to believe that some of the CP cases were initially diagnosed prior to starting our study that could have resulted in reverse causality contributing to the associations observed for CP. In addition, reverse causality could also affect aspirin–AP association, because women could have used aspirin for the pain from undiagnosed AP. Since we were not able to obtain medical records for cases, we cannot rule out the possibility of misclassification. For example, recurrent AP (RAP) may be potentially misclassified as CP. Repeated episodes of acute pancreatitis that resolve with little or no symptoms between episodes is considered RAP, while, typically, CP

results in permanent pancreatic tissue damage⁴⁶. Without medical records, it was not possible to distinguish between CP and RAP.

Lastly, this study only included women aged 65 years and older, so the results may not be generalizable to younger women or men. However, as few studies have reported on the risk factors for pancreatitis in older women, we consider the age of our study population as a strength.

Conclusions

Pancreatitis is a serious and often fatal disease. While many risk factors for pancreatitis are known, there remain many cases with unknown etiology^{8,9}. We identified several potential factors associated with AP and CP that have not been well documented previously, including high blood pressure, heart disease and HRT use. These findings suggest possible factors that are specific to elderly women and warrant further investigation.

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List of abbreviations

ACE	angiotensin-converting enzyme
AP	acute pancreatitis
BMI	Body Mass Index
CP	chronic pancreatitis
CI	confidence intervals
HRT	hormone replacement therapy
ICD-9	International Classification of Diseases, Ninth Revision
IWHS	Iowa Women's Health Study
OR	odds ratios
RAP	recurrent acute pancreatitis
SEER	Surveillance, Epidemiology, and End Results
SD	standard deviation.

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Table 1

Selected characteristics of the Iowa Women's Health Study participants.

Characteristics ^{a,b}	N	Percent %
Age at enrollment (years)		
65–66	26,763	73.5%
67–70	9,165	25.2%
>70	508	1.4%
Education		
Less than high school	7,053	19.4%
High school graduate	15,183	1.2%
Greater than high school	14,101	38.8%
BMI mean, kg/m ² (SD)		
Normal weight (<25.0)	14,441	39.6%
Overweight (25.0–29.9)	13,483	37.0%
Obese (≥ 30.0)	8,512	23.4%
Physical activity		
Inactive	16,826	47.1%
Moderately active	9,875	27.7%
Very active	8,994	25.2%
Smoking status		
Never	23,766	66.3%
Former	6,909	19.3%
Current	5,185	14.5%
Pack-years of smoking		
None	23,766	66.8%
1–19	4,823	13.6%
20–39	3,959	11.1%
40	3,008	8.5%
Alcohol consumption		
No	20,566	56.4%
Yes	15,870	43.6%
Heart disease/attack		
No	31,669	90.3%
Yes	3,412	9.7%
Diabetes		
No	34,179	93.8%
Yes	2,242	6.2%

Characteristics ^{a,b}	N	Percent %
Hypertension		
No	22,291	62.6%
Yes	13,327	37.4%
HRT use		
No	22,300	61.5%
Yes	13,971	38.5%
Aspirin use (times per week) ^b		
None	8,218	28.3%
once	9,593	33.0%
2–5	5,125	17.6%
6	6,111	21.0%

^aFrequencies may not add up to the total due to missing values

^bAll characteristics (except age at enrollment and aspirin use assessed in 1992) were assessed at baseline (1986)

Table 2

Odds ratios for acute (AP) and chronic pancreatitis (CP) across covariates 1986–2004 (n=36,436)

Characteristics	AP cases ^a (n=511)	OR (95%CI) ^c	CP cases ^a (n=149)	OR (95%CI) ^c
BMI kg/m ²				
Normal weight (<25.0)	171	1	77	1
Overweight (25.0–29.9)	205	1.29 (1.05–1.60)	46	0.67 (0.46–0.97)
Obese (≥30.0)	135	1.35 (1.07–1.70)	26	0.59 (0.37–0.94)
p-trend		0.009		0.01
Smoking status				
Never	333	1	82	1
Former	94	1.25 (0.97–1.61)	38	1.59 (1.02–2.47)
Current	78	1.02 (0.81–1.28)	28	1.64 (1.11–2.41)
p-trend		0.13		0.01
Pack-years of smoking				
None	333	1	82	1
1–19	55	0.86 (0.65–1.15)	24	1.46 (0.92–2.30)
20–39	66	1.32 (1.01–1.73)	20	1.51 (0.92–2.48)
40	46	1.25 (0.91–1.70)	20	2.03 (1.23–3.34)
p-trend		0.06		0.02
Alcohol consumption				
No	309	1	88	1
Yes	202	0.85 (0.70–1.02)	61	0.77 (0.55–1.09)
Alcohol, g/day				
0	309	1	88	1
0.5–3	91	0.79 (0.62–1.00)	30	0.85 (0.56–1.30)
>3	111	0.91 (0.72–1.15)	31	0.70 (0.45–1.08)
p-trend		0.24		0.10
Total fat intake (g/day) ^d				
48.0	99	1	23	1
48.1–63.3	109	1.19 (0.89–1.59)	39	1.91 (1.10–3.33)
63.4–82.0	127	1.41 (1.03–1.93)	40	2.11 (1.12–3.95)
82.1	125	1.53 (1.02–2.31)	30	1.80 (0.76–4.23)
p-trend		0.02		0.13
Saturated fat intake (g/day) ^d				
16.5	97	1	25	1
16.6–22.0	111	1.20 (0.90–1.60)	34	1.57 (0.91–2.72)
22.1–28.9	132	1.44 (1.07–1.95)	40	2.01 (1.11–3.66)
29.0	120	1.37 (0.94–2.01)	33	1.95 (0.89–4.25)

Characteristics	AP cases ^a (n=511)	OR (95%CI) ^c	CP cases ^a (n=149)	OR (95%CI) ^c
p-trend		0.05		0.06
Polyunsaturated fat intake (g/day) ^d				
8.1	99	1	26	1
8.2–11.0	105	1.05 (0.79–1.40)	38	1.56 (0.92–2.63)
11.1–14.5	137	1.40 (1.05–1.86)	35	1.55 (0.88–2.74)
>14.5	119	1.26 (0.89–1.79)	33	1.53 (0.76–3.07)
p-trend		0.06		0.25
Monounsaturated fat intake (g/day) ^d				
17.8	103	1		1
17.9–24.0	107	1.06 (0.80–1.41)	25	1.79 (1.05–3.07)
24.1–31.5	127	1.28 (0.95–1.72)	39	1.65 (0.89–3.07)
>31.5	123	1.29 (0.88–1.89)	33	2.09 (0.94–4.64)
p-trend		0.11	35	0.11
Protein intake (g/day) ^d				
59.0	107	1	28	1
59.1–76.3	109	1.00 (0.75–1.32)	34	1.44 (0.84–2.47)
76.4–95.9	130	1.19 (0.89–1.58)	31	1.47 (0.80–2.72)
96	114	1.05 (0.73–1.49)	39	2.30 (1.08–4.92)
p-trend		0.51		0.05
Crude fiber intake (g/day) ^d				
13.9	111	1	25	1
14.0–18.4	119	1.03 (0.78–1.34)	36	1.51 (0.88–2.56)
18.5–23.7	116	1.03 (0.78–1.36)	37	1.71 (0.98–2.97)
23.8	114	0.98 (0.72–1.33)	34	1.67 (0.87–3.21)
p-trend		0.91		0.11
Carbohydrate intake (g/day) ^d				
160.0	106	1	28	1
160.1–205.4	115	1.08 (0.82–1.42)	39	1.41 (0.84–2.38)
205.5–259.9	119	1.10 (0.82–1.48)	35	1.35 (0.75–2.44)
260	120	1.15 (0.79–1.66)	30	1.16 (0.52–2.58)
p-trend		0.47		0.66
Intake of fruits and vegetables (servings/wk) ^d				
15.50	120	1	34	1
15.54–22.49	111	0.92 (0.71–1.20)	30	0.93 (0.56–1.53)
22.50–31.48	117	0.97 (0.74–1.26)	32	0.96 (0.57–1.60)
31.5	112	0.89 (0.67–1.18)	36	1.14 (0.66–1.95)
p-trend		0.50		0.65

Characteristics	AP cases ^a (n=511)	OR (95%CI) ^c	CP cases ^a (n=149)	OR (95%CI) ^c
Intake of red meat (servings/wk) ^d				
2.50	97	1	26	1
3.00–5.00	158	1.10 (0.85–1.42)	34	0.95 (0.56–1.60)
5.25–7.50	107	1.01 (0.76–1.35)	39	1.56 (0.92–2.64)
8.00	98	0.92 (0.67–1.25)	33	1.38 (0.75–2.51)
p-trend		0.46		0.11
Heart disease/attack				
No	428	1	119	1
Yes	63	1.43 (1.09–1.88)	23	1.94 (1.23–3.06)
Diabetes				
No	478	1	140	1
Yes	32	1.01 (0.69–1.47)	9	1.20 (0.60–2.39)
Hypertension				
No	274	1	84	1
Yes	226	1.37 (1.14–1.65)	64	1.47 (1.05–2.07)
HRT use				
No	289	1	64	1
Yes	219	1.18 (0.99–1.41)	82	1.97 (1.42–2.75)
Aspirin use (times per week) ^b				
None	94	1	30	1
once	107	1.01 (0.76–1.33)	26	0.72 (0.42–1.23)
2–5	75	1.30 (0.95–1.77)	12	0.65 (0.33–1.26)
6	102	1.44 (1.08–1.91)	25	1.11 (0.65–1.89)
p-trend		0.04		0.80

^aNumber of AP and CP cases may differ for different variables due to missing values

^bAssessed in 1992

^cAll models were adjusted for age and the time of Medicare enrollment. The models for BMI and smoking (status and pack-years) were adjusted for each other. All other models were additionally adjusted for BMI, smoking status and pack-years of smoking.

^dAll dietary variables were assessed after (1) excluding people with unreliable dietary data so that there were 132 CP cases and 460 AP cases among 33,183 IWHs participants and (2) additional adjustment for total energy intake.