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Brief communication

Risk factors for pancreatitis in older women: the Iowa Women's Health Study

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ABSTRACT

Purpose: Pancreatitis—an inflammation of pancreas—is a severe and costly disease. Although many risk factors for pancreatitis are known, many pancreatitis cases, especially in elderly women, are of unknown etiology. *Methods*: Risk factors for acute pancreatitis (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 follows: "AP", one AP episode (n = 511) or "CP", 2+ AP or 1+ CP episodes (n = 149). *Results*: Multivariable odds ratios (ORs) and 95% confidence intervals for AP and CP were calculated using

multinomial logistic regression. Alcohol use was not associated with AP or CP. Heavy smoking (40+ vs. 0 pack-years) was associated with a twofold increased OR for CP. For body mass index greater than or equal to 30 versus less than 25 kg/m², the ORs were 1.35 (1.07–1.70) for AP (P trend = .009) and 0.59 (0.37–0.94) for CP (P trend = .01). ORs for AP and CP were increased for hormone replacement therapy 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. © 2015 Elsevier Inc. All rights reserved.

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 pancreas [2].

Pancreatitis can be acute pancreatitis (AP), with sudden onset and usually resolving within several days, or chronic pancreatitis (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 damage [2]. Diagnosing

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pancreatitis (AP or CP) may be difficult; it requires that two of three criteria (clinical presentation with abdominal pain, elevated amylase or lipase, or radiographic evidence) be met [3]. Symptoms of an exacerbation of CP are often the same as AP [4].

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 aged 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 postmenopausal women aged 55 to 69 years were recruited at







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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 factors [10]. Annual linkage to the Iowa Surveillance, Epidemiology, and End Results registry provided cancer incidence, whereas linkage to the National Death Index provided mortality [10]. The University of Minnesota Institutional Review Board approved this study, and all participants gave consent.

The data for IWHS participants older than 65 years were linked to Centers for Medicare Services claims (1986-2004) by social security number, first and last name, and date of birth [11], as U.S. residents become eligible for Medicare at 65 years. Linkage to participants older than 65 years was successful for 99% of the cohort members alive at 65 years [12]. Pancreatitis cases were ascertained through Medicare hospital, carrier, and outpatient claims [13]. Women with one or more hospitalizations or greater than or equal to two claims from the outpatient or carrier files with an International Classification of Diseases, Ninth Revision 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, that is, cases with insufficient data to confirm pancreatitis. Pancreatitis cases were categorized as AP, if women had one AP episode and CP, if women had two or more episodes of AP that were at least 6 weeks apart or one episode of CP. Also, women were excluded if their first pancreatitis episode was within ± 6 months of Surveillance, Epidemiology, and End Results-identified gastrointestinal cancer.

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

All models were adjusted for age at 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. ORs and *P* values for trend were computed using SAS software, Version [9.3] of the SAS System for Windows. 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 \pm 1.6 years; 99.2% white). The mean ages of the AP and CP diagnosis were 75.3 \pm 5.5 and 73.3 \pm 5.5 years, respectively. At baseline, 23% of the cohort were obese, 14% were current smokers, and 43% consumed alcohol (Table 1).

Cigarette smoking was associated with CP for more than 40 versus 0 pack-years with an OR = 2.03 (95% CI: 1.23–3.34; *P* trend = .02). BMI was positively associated with AP and inversely associated with CP; for BMI greater than or equal to 30 versus less than 25 kg/m², the ORs were 1.35 (95% CI: 1.07–1.70; *P* trend = .009) and 0.59 (95% CI: 0.37–0.94; *P* trend = .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/wk and AP, OR = 1.44 (95% CI: 1.08–1.91) versus no aspirin use (*P* trend = .04). We did not observe

Table 1

Selected characteristics of the IWHS participants

Age at enrollment (y) Second s	Characteristics ^{*,†}	Ν	%
65-66 26,763 73.5 67-70 9165 25.2 >70 508 1.4 Education 1 1 Less than high school 7053 19.4 High school graduate 15,183 1.2 Greater than high school 14,101 38.8 BMI mean, kg/m² (SD) Normal weight (<25.0)	Age at enrollment (y)		
67-70 9165 25.2 >70 508 1.4 Education	65-66	26,763	73.5
>70 508 1.4 Education	67-70	9165	25.2
Education 7053 19.4 Less than high school 7053 19.4 High school graduate 15,183 1.2 Greater than high school 14,101 38.8 BMI mean, kg/m² (SD) 14,441 39.6 Normal weight (<25.0)	>70	508	1.4
Less than high school 7053 19.4 High school graduate 15,183 1.2 Greater than high school 14,101 38.8 BMI mean, kg/m² (SD) 14,441 39.6 Normal weight (<25.0)	Education		
High school graduate15,1831.2Greater than high school14,10138.8BMI mean, kg/m² (SD)	Less than high school	7053	19.4
Greater than high school 14,101 38.8 BMI mean, kg/m² (SD)	High school graduate	15,183	1.2
BMI mean, kg/m ² (SD) 14,441 39.6 Normal weight (<25.0)	Greater than high school	14,101	38.8
Normal weight (<25.0)	BMI mean, kg/m ² (SD)		
Overweight (25.0-29.9) 13,483 37.0 Obese (≥30.0) 8512 23.4 Physical activity 16,826 47.1 Inactive 16,826 47.1 Moderately active 9875 27.7 Very active 8994 25.2 Smoking status 8994 25.2 Smoking status 16,826 66.3 Former 6909 19.3 Current 5185 14.5 Pack-years of smoking 8 1.5 None 23,766 66.8 1-19 4823 13.6 20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption 10 43.6 No 20,566 56.4 Yes 3412 9.7 Diabetes 1 93.8 Yes 24.1 9.7 No 34,179 93.8 Yes 13,327 37.4 HRT use 13,3	Normal weight (<25.0)	14,441	39.6
Obese (≥30.0) 8512 23.4 Physical activity Inactive 16,826 47.1 Moderately active 9875 27.7 Very active 8994 25.2 Smoking status 8994 25.5 Never 23,766 66.3 Former 6909 19.3 Current 5185 14.5 Pack-years of smoking 14.5 14.5 None 23,766 66.8 1-19 4823 13.6 20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption 7 7 No 20,566 56.4 Yes 3412 9.7 Diabetes 7 73.8 No 34,179 93.8 Yes 22,291 62.6 Yes 13,327 37.4 Hypertension 7 7 No 22,300 61.5 Yes 13,971	Overweight (25.0–29.9)	13,483	37.0
Physical activity Inactive 16,826 47.1 Moderately active 9875 27.7 Very active 8994 25.2 Smoking status	Obese (≥30.0)	8512	23.4
Inactive 16,826 47.1 Moderately active 9875 27.7 Very active 8994 25.2 Smoking status	Physical activity		
Moderately active 9875 27.7 Very active 8994 25.2 Smoking status 23,766 66.3 Never 23,766 66.3 Former 6909 19.3 Current 5185 14.5 Pack-years of smoking None 23,766 66.8 1−19 4823 13.6 20−39 3959 11.1 ≥40 3008 8.5 Alcohol consumption No 20,566 56.4 Yes 15,870 43.6 Heart disease/attack No 31,669 90.3 Yes 3412 9.7 Diabetes No 34,179 93.8 Yes 22,291 62.6 Yes 13,327 37.4 HRT use No 22,300 61.5 Yes	Inactive	16,826	47.1
Very active 8994 25.2 Smoking status	Moderately active	9875	27.7
Smoking status Never 23,766 66.3 Former 6909 19.3 Current 5185 14.5 Pack-years of smoking None 23,766 66.8 1-19 4823 13.6 20–39 3959 11.1 ≥40 3008 8.5 Alcohol consumption No 20,566 56.4 Yes 15,870 43.6 Heart disease/attack No 31,669 90.3 Yes 3412 9.7 Diabetes No 34,179 93.8 Yes 22,291 62.6 Hypertension No 22,291 62.6 Yes 13,327 37.4 HRT use None 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) ¹ None 8218 <td>Verv active</td> <td>8994</td> <td>25.2</td>	Verv active	8994	25.2
Never 23,766 66.3 Former 6909 19.3 Current 5185 14.5 Pack-years of smoking 66.8 1–15 None 23,766 66.8 1-19 4823 13.6 20–39 3959 11.1 ≥40 3008 8.5 Alcohol consumption 7 7 No 20,566 56.4 Yes 15,870 43.6 Heart disease/attack 7 7 No 31,669 90.3 Yes 3412 9.7 Diabetes 7 7 No 34,179 93.8 Yes 2242 62.6 Yes 22,291 62.6 Yes 13,327 37.4 HRT use 7 7 None 22,300 61.5 Yes 13,327 37.4 None 8218 28.3 ≤Once	Smoking status		
Former 6909 19.3 Current 5185 14.5 Pack-years of smoking None 23,766 66.8 1-19 4823 13.6 20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption No 20,566 56.4 Yes 25,567 43.6 Heart disease/attack No 31,669 90.3 Yes 3412 9.7 Diabetes No 34,179 93.8 Yes 34,179 93.8 Yes 34,179 93.8 Yes 22,291 62.6 Hypertension No 22,291 62.6 Yes 13,327 37.4 HRT use None 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) ¹ <t< td=""><td>Never</td><td>23,766</td><td>66.3</td></t<>	Never	23,766	66.3
Current 5185 14.5 Pack-years of smoking	Former	6909	19.3
Pack-years of smoking None 23,766 66.8 1-19 4823 13.6 20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption 0 20,566 56.4 Yes 15,870 43.6 Heart disease/attack 0 31,669 90.3 Yes 3412 9.7 Diabetes 0 34,179 93.8 Yes 2242 6.2 Hypertension 0 22,291 62.6 Yes 13,327 37.4 HRT use 0 22,300 61.5 Yes 13,327 37.4 HRT use 0 22,301 63.5 Yes 13,971 38.5 Aspirin use (times/wk) ¹ 0 22,300 61.5 None 8218 28.3 20.0 ≤Once 9593 33.0 25 5125 17.6 > 6 5125 17.6 5125 17.6	Current	5185	14.5
None 23,766 66.8 1-19 4823 13.6 20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption 0 20,566 56.4 Yes 15,870 43.6 Heart disease/attack 0 31,669 90.3 Yes 3412 9.7 Diabetes No 34,179 93.8 Yes 2242 6.2 Hypertension 0 22,291 62.6 Yes 13,327 37.4 HRT use 0 22,300 61.5 Yes 13,327 37.4 None 22,300 61.5 Yes 3.07 38.5 Aspirin use (times/wk) ¹ 0 22,300 61.5 Yes 3.00 2–5 5125 17.6 5125 17.6	Pack-years of smoking		
1-19 4823 13.6 20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption 0 20,566 56.4 Yes 15,870 43.6 Heart disease/attack 0 31,669 90.3 Yes 3412 9.7 Diabetes 0 34,179 93.8 Yes 2242 62.6 Hypertension 0 22,291 62.6 Yes 13,327 37.4 HRT use 0 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) ¹ 0 30.2 None 8218 28.3 ≤Once 9593 33.0 2-5 5125 17.6	None	23.766	66.8
20-39 3959 11.1 ≥40 3008 8.5 Alcohol consumption No 20,566 56.4 Yes 15,870 43.6 Heart disease/attack No 31,669 90.3 Yes 3412 9.7 Diabetes No 34,179 93.8 Yes 2242 62.6 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/wk) ¹ None 8218 28.3 ≤Once 9593 33.0 2–5 5125 17.6 >6 5121 17.6	1-19	4823	13.6
≥40 3008 8.5 Alcohol consumption 7 No 20,566 56.4 Yes 15,870 43.6 Heart disease/attack 7 No 31,669 90.3 Yes 3412 9.7 Diabetes 7 No 34,179 93.8 Yes 2242 62.6 Hypertension 7 7.4 No 22,291 62.6 Yes 13,327 37.4 HRT use 7 7.4 No 22,300 61.5 Yes 22,301 38.5 Aspirin use (times/wk) ¹ 8218 28.3 ≤Once 9593 33.0 2-5 5125 17.6 > 6 5125 17.6	20-39	3959	11.1
Alcohol consumption 000 000 No 20,566 56.4 Yes 15,870 43.6 Heart disease/attack 07 No 31,669 90.3 Yes 3412 9.7 Diabetes 0 3412 9.7 Diabetes 0 34,179 93.8 Yes 2242 6.2 Hypertension 0 22,291 62.6 Yes 13,327 37.4 HRT use 0 22,300 61.5 No 22,300 61.5 38.5 Aspirin use (times/wk) [†] 0 22,300 61.5 None 8218 28.3 $\leq Once$ 9593 33.0 2–5 5125 17.6 5125 17.6	>40	3008	8.5
No20,56656.4Yes15,87043.6Heart disease/attack V No31,66990.3Yes34129.7Diabetes V No34,17993.8Yes22426.2Hypertension V No22,29162.6Yes13,32737.4HRT use V V No22,30061.5Yes13,97138.5Aspirin use (times/wk) [†] V V None821828.3 \leq Once959333.02-5512517.6 ≥ 6 611121.2	Alcohol consumption		
Yes15,87043.6Heart disease/attack 1669 90.3No31,66990.3Yes34129.7Diabetes 1412 9.7No34,17993.8Yes22426.2Hypertension $13,327$ 37.4No22,29162.6Yes13,32737.4HRT use $13,327$ 37.4No22,30061.5Yes13,97138.5Aspirin use (times/wk) ¹ 1202 None821828.3≤Once959333.02-5512517.6> 6611131.2	No	20.566	56.4
Heart disease/attack Intervention No 31,669 90.3 Yes 3412 9.7 Diabetes 900 93.8 No 34,179 93.8 Yes 2242 6.2 Hypertension 13,327 37.4 No 22,291 62.6 Yes 13,327 37.4 HRT use 1 1 No 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) ¹ 1 1 None 8218 28.3 ≤Once 9593 33.0 2-5 5125 17.6 >6 6111 17.2	Yes	15.870	43.6
No $31,669$ 90.3 Yes 3412 9.7 Diabetes V No $34,179$ 93.8 Yes 2242 62.6 Hypertension V $22,291$ 62.6 Yes $13,327$ 37.4 HRT use V $13,327$ 37.4 HRT use V $13,971$ 38.5 Aspirin use (times/wk) [†] V V $22,300$ 61.5 None 8218 28.3 20 20.5 33.0 $2-5$ 5125 17.6 5125 17.6	Heart disease/attack	,	
Yes 3412 9.7 Diabetes 9.7 No 34,179 93.8 Yes 2242 6.2 Hypertension 0 22,291 No 22,291 62.6 Yes 13,327 37.4 HRT use 0 22,300 No 22,300 61.5 Yes 13,927 38.4 None 22,300 61.5 Aspirin use (times/wk) ¹ 0 0 None 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6 >6 111 17.2	No	31.669	90.3
Diabetes 0.11 No $34,179$ Yes 2242 Hypertension 0.0 No $22,291$ G2.6 Yes Yes $13,327$ ART use 0.0 No $22,300$ G1.5 Yes No $22,300$ G1.5 Yes No $22,300$ Solution 38.5 Aspirin use (times/wk) [†] 10 None 8218 $\leq Once$ 9593 $2-5$ 5125 $2-5$ 5125 $20,200$ 712	Yes	3412	97
No $34,179$ 93.8 Yes 2242 6.2 Hypertension $22,291$ 62.6 No $22,291$ 62.6 Yes $13,327$ 37.4 HRT use $22,300$ 61.5 No $22,300$ 61.5 Yes $13,971$ 38.5 Aspirin use (times/wk) [†] V V None 8218 28.3 $\leq Once$ 9593 33.0 $2-5$ 5125 17.6	Diabetes	3112	517
Yes 2242 6.2 Hypertension 6.2 No 22,291 62.6 Yes 13,327 37.4 HRT use 7 7 No 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) [†] 7 7 None 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6 \geq 6 6111 212	No	34,179	93.8
Hypertension 122,291 62.6 No 22,291 62.6 Yes 13,327 37.4 HRT use 22,300 61.5 No 22,301 38.5 Aspirin use (times/wk) ¹ 30.0 2 None 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6	Yes	2242	6.2
No 22,291 62.6 Yes 13,327 37.4 HRT use 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) [†] 7 7 None 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6	Hypertension		
Yes 13,327 37.4 HRT use 7 7 No 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) [†] 7 7 None 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6 \geq 6 C111 21.2	No	22.291	62.6
HRT use 15/22 31.1 No 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) [†] 8218 28.3 $\leq Once$ 9593 33.0 2-5 5125 17.6 > 6 C111 21.2	Yes	13 327	37.4
No 22,300 61.5 Yes 13,971 38.5 Aspirin use (times/wk) [†] $\overline{}$ $\overline{}$ None 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6 \geq 6 C111 21.2	HRTuse	10,027	5711
Yes 13,971 38.5 Aspirin use (times/wk) [†] 8218 28.3 \leq Once 9593 33.0 2-5 5125 17.6 \geq 6 6111 212	No	22 300	61.5
Aspirin use (times/wk) [†] Basic None 8218 28.3 $\leq Once$ 9593 33.0 $2-5$ 5125 17.6 ~ 6 $C111$ 212	Yes	13.971	38.5
None 8218 28.3 ≤Once 9593 33.0 2-5 5125 17.6	Aspirin use $(times/wk)^{\dagger}$	10,071	5015
≤Once 9593 33.0 2−5 5125 17.6	None	8218	28.3
2-5 5125 17.6	<once< td=""><td>9593</td><td>33.0</td></once<>	9593	33.0
	2-5	5125	17.6
≥o 011 210	>6	6111	21.0

* Frequencies may not add up to the total because of missing values.

[†] All characteristics (except age at enrollment and aspirin use assessed in 1992) were assessed at baseline (1986).

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 older than 65 years, we confirmed several known risk factors for pancreatitis. Consistent with previous studies [1,14], heavy cigarette smoking (40+ vs. 0 pack-years) was associated with a twofold increased risk for CP, whereas 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 pancreatitis [1]. As gallstone disease is common in obese people, it may mediate the obesity–AP association [17]. Furthermore, in our study, BMI was inversely associated with CP, which is most likely

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