

# Smoking and Risk of Acute and Chronic Pancreatitis Among Women and Men

## A Population-Based Cohort Study

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**Background:** Alcohol and gallstone disease are the most established risk factors for pancreatitis. Smoking is rarely considered to be a cause despite the fact that a few studies have indicated the opposite. We aimed to assess the independent effects of smoking on the risk of pancreatitis.

**Methods:** We used data from an observational, population-based cohort study conducted in Denmark. Participants were 9573 women and 8332 men who were followed up for a mean of 20.2 years. Participants underwent a physical examination and completed self-administered questionnaires about lifestyle habits. Information on incident cases of acute and chronic pancreatitis were obtained by record linkage with the Danish national registries.

**Results:** A total of 235 cases of pancreatitis occurred during follow-up. A dose-response association between smok-

ing and risk of acute and chronic pancreatitis was observed in both men and women. For example, the hazard ratio of developing pancreatitis was 2.6 (95% confidence interval [CI], 1.5-4.7) among women and 2.6 (95% CI, 1.1-6.2) among men who smoked 15 to 24 grams of tobacco per day. Alcohol intake was associated with an increased risk of pancreatitis (hazard ratio, 1.09; 95% CI, 1.04-1.14 for each additional drink per day). The risk of pancreatitis associated with smoking, however, was independent of alcohol and gallstone disease. Approximately 46% of cases of pancreatitis were attributable to smoking in this cohort.

**Conclusion:** In this population of Danish men and women, smoking was independently associated with increased risk of pancreatitis.

*Arch Intern Med.* 2009;169(6):603-609

**T**HE INCIDENCE OF PANCREATITIS has increased in recent decades.<sup>1-8</sup> Pancreatitis can be divided into acute and chronic pancreatitis; however, disagreement exists on whether 2 distinct conditions really exist or whether acute pancreatitis leads to chronic pancreatitis.<sup>9,10</sup> The most common symptom of both is severe abdominal pain. The mortality rate of acute pancreatitis is especially high and has not decreased since the 1970s, which is most likely because treatment has not improved and is mainly directed toward pain control.

Gallstone disease and excessive alcohol use are described as being the most common causes of acute and chronic pancreatitis, respectively. In the medical literature, smoking is generally not considered to be an important risk factor for pancreatitis, even though some case-control studies conducted in men, as well as a recent cohort study, suggest the opposite.<sup>11-18</sup> Also, evidence from experimental studies<sup>19-22</sup> sug-

gests that smoking is associated with pancreas damage. In most populations, smoking is strongly associated with drinking alcohol; hence, an independent effect of smoking can be difficult to assess, especially from a case-control design because individuals with moderate to heavy alcohol intake are dominant.

Smoking may also be associated with risk of gallstone disease.<sup>23,24</sup> If so, observed associations between smoking and pancreatitis could be explained by an increased risk of gallstones in individuals who smoke, which in turn renders these individuals at high risk of pancreatitis.

In this study, we examined the association between smoking and risk of acute and chronic pancreatitis in a large prospective cohort consisting of men and women from the general population. Our objective was to determine if smoking is associated with an increased risk of acute and chronic pancreatitis independently of alcohol use and gallstone disease.

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## STUDY POPULATION

Data used in this study came from the first 3 examinations of the Copenhagen City Heart Study (CCHS), performed in 1976-1978, 1981-1983, and 1991-1994. The CCHS is a prospective cohort study. The participants were randomly chosen from the general population of Copenhagen and included 14 233 men and women 20 to 95 years old in 1976-1978 (response rate, 74%). In 1981-1983, all previously invited individuals plus 500 new individuals aged 20 to 24 years were invited to participate, resulting in 12 698 participants (response rate, 70%). In 1991-1994, all previously invited individuals plus 3000 new individuals aged 20 to 49 years were invited to participate, and 10 135 of these participated (response rate, 61%). In total, 18 035 individuals participated in 1 or more examinations of the CCHS.

Before visiting the study clinic, participants completed a self-administered questionnaire (including questions on alcohol intake, smoking, physical activity, education level, and income). At the clinic visit, physical examinations were performed (including measurement of height, weight, forced expiratory volume in 1 second [FEV<sub>1</sub>], and carbon dioxide in expired air) and questionnaires were checked for missing information.

## SMOKING

At each examination, participants were asked whether they smoked or had been smoking previously and, if the response was affirmative, about duration of smoking (in years). Current smokers were further asked about the usual amount of tobacco in categories of daily cigarettes, cheroots, cigars, and pipes. Assuming 1 cigarette to be equivalent to 1 g of tobacco, 1 cheroot or 1 pipe to 3 g of tobacco, and 1 cigar to 5 g of tobacco, participants were categorized in 5 groups (never-smokers, ex-smokers, and smokers of 1-14, 15-24, and >24 g/d of tobacco). Pack-years of smoking were calculated as (years of smoking × daily grams of tobacco)/20. For current smokers, duration of smoking was updated every 5 years until the participant reported having quit or was censored. For ex-smokers, we had information only on duration of smoking; therefore, pack-years could not be calculated.

## COVARIABLES

For the purpose of this study, sex, smoking, education level, income, body mass index (BMI), and physical activity were considered potential confounders. Education level was categorized as less than 8 years, 8 to 11 years, and more than 11 years of education corresponding to lower primary school, higher primary school, and secondary school, respectively. Income was categorized as low, middle, and high income. The BMI was calculated as weight in kilograms divided by height in meters squared (measured at the clinic visit) and thereafter categorized as less than 20, 20 through 24.9, and 25 or greater. Physical activity was categorized as sedentary (light physical activity for <2 hours per week), light (light physical activity for 2-4 hours per week), moderate (light physical activity for >4 hours per week or strenuous activity for 2-4 hours per week), and heavy (strenuous physical activity at least 4 hours per week). Concerning alcohol intake, participants were asked how often they drank beer, wine, and spirits in categories of "never/hardly ever," "monthly," "weekly," and "daily" and how many drinks they drank of each type of beverage per week. The 3 types of alcoholic beverage were added up to a measure of total alcohol intake.

Information on pancreatitis was obtained from the Danish Hospital Discharge Register<sup>25</sup> and the Danish Registers of Causes of Death,<sup>26</sup> which contain data on all hospital admissions and causes of death in Denmark, respectively. Information on incident cases of pancreatitis among the study participants in these registries was identified through linkage by the unique identification number, which is allocated to every Danish inhabitant by the Central Population registry. The exact diagnosis for pancreatitis has not been validated, but the validity of the Danish Hospital Discharge Register is generally considered to be high.<sup>27</sup> For acute pancreatitis, the relevant *International Classification of Diseases, Eighth Revision (ICD-8)*<sup>28</sup> codes were 577.00, 577.01, 577.02, 577.03, 577.04, 577.08, and 577.09, along with *International Statistical Classification of Diseases, 10th Revision (ICD-10)*<sup>29</sup> code K85.9. For chronic pancreatitis, the relevant ICD-8 codes were 577.19, 577.90, 577.91, and 577.92, and the ICD-10 codes were K86.0, K86.1, K86.2, K86.3, and K86.9. Lastly, information on gallstone disease was also obtained from the Danish Hospital Discharge Register (ICD-8 and ICD-10 code K80).

## STATISTICAL ANALYSIS

Participants accrued person-time from the time of their first participation in the CCHS until the time of their first admission to a hospital because of pancreatitis, date of death, emigration, or end of follow-up (July 9, 2007), whichever occurred first. We had follow-up information on 100% of the study participants. Analyses were performed for acute and chronic pancreatitis separately and combined (total pancreatitis). For the analysis of acute pancreatitis, participants who had a previous diagnosis of chronic pancreatitis were censored at the time of the chronic pancreatitis (n=11). Participants with missing information on smoking, alcohol intake, BMI, or school education level (n=125) or with a diagnosis of pancreatitis before baseline (n=3) were excluded from the study, which left 17 905 eligible for analysis. Data were analyzed by means of the Cox proportional hazards regression model, with delayed entry implemented (using the SAS/STAT program software, version 9.1; SAS Institute Inc, Cary, North Carolina). To ensure maximal adjustment for confounding by age, age (in days) was used as the underlying time axis. The Cox proportional hazards assumption was examined graphically and statistically by introducing interaction terms between time and alcohol consumption in the model; no violations against the assumptions were detected.

Primary analyses were performed using updated measures of alcohol consumption and other covariables, in which we prospectively assessed the risk of pancreatitis in between-examination increments, based on information on alcohol consumption and other covariables derived from the preceding questionnaire. Also, analyses were performed including only information on smoking and covariables from the first examination in which every participant had joined.

We estimated the population-attributable risk related to smoking categories (never-smoker, ex-smoker, and current smokers of 1-14, 15-24, and ≥25 g/d of tobacco) as  $\sum P_{ei} (RR_i - 1) / 1 + \sum P_{ei} (RR_i - 1)$ , where  $P_{ei}$  is the prevalence of the  $i$ th smoking category and  $RR_i$  is the relative risk associated with this category.<sup>30</sup>

Interaction between alcohol intake and smoking was determined with the use of a nested log-likelihood test, comparing a model containing the variables as single terms with a model also including the interaction terms. For this particular purpose, alcohol was categorized into 3 groups (<7, 7-20, and >20 drinks per week) and smoking was categorized into 2 groups

**Table 1. Baseline Characteristics of 9573 Women and 8332 Men Participating in the Copenhagen City Heart Study by Smoking Status<sup>a</sup>**

Characteristic	All Patients	Smoking Status				
		Never	Former	1-14 g/d of Tobacco	15-24 g/d of Tobacco	≥25 g/d of Tobacco
<b>Women</b>						
No. (%)	9573	2665 (28)	1430 (15)	2843 (30)	2255 (24)	380 (4)
Mean age (range), y	52 (26-70)	53 (25-72)	53 (27-72)	53 (27-69)	48 (27-66)	51 (31-67)
Duration of smoking, y	25 (5-43)		11 (2-40)	25 (6-45)	25 (10-43)	29 (10-44)
FEV <sub>1</sub> , % predicted	80 (63-94)	82 (68-95)	81 (64-93)	80 (61-93)	79 (61-93)	79 (59-93)
Carbon dioxide in expired air, ppm	3 (1-25)	2 (1-4)	2 (1-4)	8 (2-22)	15 (3-32)	19 (2-41)
Alcohol intake, drinks/wk <sup>b</sup>	3 (0-16)	2 (0-13)	3 (0-16)	3 (0-16)	3 (0-21)	5 (0-38)
BMI	24 (19-33)	24 (19-34)	24 (19-34)	23 (19-32)	23 (19-32)	24 (19-33)
Physical inactivity, %	19	17	14	18	23	28
Low income, %	33	36	30	34	30	29
Education level <8 y, %	43	41	37	47	45	38
<b>Men</b>						
No. (%)	8332	1080 (13)	1597 (19)	1950 (23)	2542 (31)	1163 (14)
Mean age (range), y	52 (26-70)	41 (23-69)	56 (30-73)	54 (26-73)	51 (28-69)	50 (33-68)
Duration of smoking, y	30 (7-53)		22 (2-50)	34 (8-57)	33 (10-51)	34 (15-52)
FEV <sub>1</sub> , % predicted	79 (59-94)	82 (69-96)	80 (60-94)	79 (57-95)	78 (57-94)	78 (58-94)
Carbon dioxide in expired air, ppm	4 (1-28)	2 (1-5)	2 (1-5)	7 (2-23)	14 (3-33)	17 (5-41)
Alcohol intake, drinks/wk <sup>b</sup>	11 (0-49)	8 (0-36)	11 (0-42)	10 (0-42)	12 (0-51)	18 (0-77)
BMI	25 (20-32)	25 (20-32)	26 (21-33)	25 (20-32)	25 (20-32)	26 (21-33)
Physical inactivity, %	19	13	17	16	21	27
Low income, %	24	24	25	28	23	17
Education level <8 y, %	42	27	43	45	46	45

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FEV<sub>1</sub>, forced expiratory volume in 1 second.

<sup>a</sup>Data are medians (5th-95th percentiles) unless otherwise indicated.

<sup>b</sup>One drink corresponds to 12 g of pure alcohol.

(never-smokers and ex-smokers and current smokers) to increase the statistical power of the test.

## RESULTS

### BASELINE CHARACTERISTICS

**Table 1** gives the characteristics of 17 905 men and women categorized by smoking status as reported at the time of their first participation in the CCHS (1976-1978, 1981-1983, or 1991-1994). Overall, 58% of the women and 68% of the men were current smokers, 15% of the women and 19% of the men were ex-smokers, and 28% of the women and 13% of the men had never smoked. As expected, lung function as measured by FEV<sub>1</sub> (in percentage of the expected value) was highest in participants who never smoked and was lowest in participants who were current smokers. Also, carbon dioxide in expired air was similar in never-smokers and ex-smokers and increased with increasing amounts of tobacco used per day. On average, current smokers drank more alcohol and were less physically active compared with never-smokers.

### SMOKING STATUS, PACK-YEARS, AND RISK OF PANCREATITIS

The mean follow-up in this study was 20.2 years (range, 0-28.3 years). At the end of follow-up, a total of 235 participants (113 women and 122 men) had developed pancreatitis, and there were 160 cases of acute and 97 cases

of chronic pancreatitis (the number of cases of acute and chronic pancreatitis does not equal the total number of cases because some people had both acute and chronic pancreatitis and they were only counted once in the total number of cases).

We performed analyses by modeling the risk of acute and chronic pancreatitis combined (total pancreatitis) according to categories of smoking status (**Table 2**). Similar risk estimates were observed in women and men: for example, the hazard ratio of developing pancreatitis was 2.6 (95% confidence interval [CI], 1.5-4.7) among women and 2.6 (95% CI, 1.1-6.2) among men who smoked 15 to 24 grams per day of tobacco. Combining women and men (*P* value for interaction between sex and smoking status in nested log likelihood test was .70) in an analysis adjusted for age and sex and in an analysis further adjusted for alcohol, education level, and BMI, current smokers had a higher risk of both acute and chronic pancreatitis compared with never-smokers, and risk estimates were similar for the 2 outcomes (**Table 3**). For ex-smokers, however, the hazard ratio for acute pancreatitis was 2.3 (95% CI, 1.3-4.1), whereas the hazard ratio for chronic pancreatitis was 0.9 (95% CI, 0.4-2.0). For total pancreatitis, adjusted hazard ratios were 1.7 (95% CI, 1.0-2.7), 1.5 (95% CI, 0.9-2.5), 2.5 (95% CI, 1.5-3.9), and 3.3 (95% CI, 1.9-5.8) among ex-smokers and current smokers of 1 to 14, 15 to 24, and 25 g/d or more of tobacco, respectively. In the multivariable-adjusted models, alcohol was responsible for most of the effect of adjustment. The adjusted hazard ratio for amount of alcohol intake was 1.09

**Table 2. Risk of Total Pancreatitis by Updated Information on Smoking Status in Men and Women<sup>a</sup>**

	Smoking Status				
	Never	Former	1-14 g/d of Tobacco	15-24 g/d of Tobacco	≥25 g/d of Tobacco
<b>Women</b>					
No. of cases	20	23	30	35	5
Crude hazard ratio (95% CI)	1.0	1.4 (0.8-2.5)	1.7 (1.0-3.0)	2.8 (1.6-5.0)	2.5 (0.9-6.6)
Adjusted hazard ratio (95% CI) <sup>b</sup>	1.0	1.4 (0.8-2.6)	1.7 (0.9-3.0)	2.6 (1.5-4.7)	2.3 (0.8-6.2)
<b>Men</b>					
No. of cases	6	31	18	37	30
Crude hazard ratio (95% CI)	1.0	2.2 (0.9-5.4)	1.6 (0.6-4.1)	2.9 (1.2-6.7)	4.9 (2.0-12.0)
Adjusted hazard ratio (95% CI) <sup>b</sup>	1.0	2.1 (0.9-5.2)	1.5 (0.6-3.9)	2.6 (1.1-6.2)	4.1 (1.7-9.9)

Abbreviation: CI, confidence interval.

<sup>a</sup>Results from Cox proportional hazards regression analysis with age as the underlying time scale.

<sup>b</sup>Adjusted for education level (<8 years, 8-11 years, >11 years), body mass index (calculated as weight in kilograms divided by height in meters squared; <20, 20-24.9, ≥25), and alcohol intake (continuous).

**Table 3. Risk of Acute, Chronic, and Total Pancreatitis by Updated Information on Smoking Status in Men and Women Combined<sup>a</sup>**

	Smoking Status				
	Never	Former	1-14 g/d of Tobacco	15-24 g/d of Tobacco	≥25 g/d of Tobacco
<b>Acute pancreatitis</b>					
No. of cases	16	45	34	44	21
Crude hazard ratio (95% CI)	1.0	2.4 (1.3-4.2)	1.9 (1.1-3.5)	2.8 (1.6-5.1)	4.3 (2.2-8.5)
Adjusted hazard ratio (95% CI) <sup>b</sup>	1.0	2.3 (1.3-4.1)	2.0 (1.1-3.6)	2.8 (1.5-5.0)	3.8 (1.9-7.5)
<b>Chronic pancreatitis</b>					
No. of cases	11	13	18	34	21
Crude hazard ratio (95% CI)	1.0	0.9 (0.4-2.0)	1.3 (0.6-2.7)	2.4 (1.2-4.9)	4.2 (1.9-9.0)
Adjusted hazard ratio (95% CI) <sup>b</sup>	1.0	0.9 (0.4-2.0)	1.1 (0.5-2.3)	2.0 (1.0-4.1)	3.3 (1.5-7.3)
<b>Total pancreatitis</b>					
No. of cases	26	54	48	72	35
Crude hazard ratio (95% CI)	1.0	1.7 (1.0-2.7)	1.6 (1.0-2.6)	2.6 (1.7-4.1)	3.9 (2.3-6.7)
Adjusted hazard ratio (95% CI) <sup>b</sup>	1.0	1.7 (1.0-2.7)	1.5 (0.9-2.5)	2.5 (1.5-3.9)	3.3 (1.9-5.8)

Abbreviation: CI, confidence interval.

<sup>a</sup>Results from Cox proportional hazards regression analysis with age as the underlying time scale.

<sup>b</sup>Adjusted for sex, education level (<8 years, 8-11 years, >11 years), body mass index (calculated as weight in kilograms divided by height in meters squared; <20, 20-24.9, ≥25), and alcohol intake (continuous).

(96% CI, 1.04-1.14) for each additional drink per day. The inclusion of variables for personal income and physical activity to the fully adjusted model had negligible effect on the size and precision of the risk estimates. The fully adjusted risk of pancreatitis in women compared with men was 0.9 (95% CI, 0.6-1.1). Repeating the analyses without updating information on smoking and other variables did not change our results (data not shown).

To explore if the relatively high risk among ex-smokers was due to sick-quitters (ie, participants who have given up smoking because of early symptoms of pancreatitis), we performed additional analyses omitting the first 2 variables for follow-up and updating smoking variables and covariables with a delay of 2 years. However, this only affected risk estimates slightly. Compared with the hazard ratio estimated for the entire follow-up period (1.7; 95% CI, 1.0-2.7), the hazard ratio was 1.6 (95% CI, 1.0-2.6) when omitting the first 2 years of follow-up.

Hazard ratios of acute, chronic, and total pancreatitis according to pack-years of smoking for current smokers and smoking duration for ex-smokers are given in

**Table 4.** Dose-response associations were observed and again the associations for risk of acute and chronic pancreatitis were similar. For example, hazard ratios of acute and chronic pancreatitis were 3.2 (95% CI, 1.6-6.2) and 3.1 (95% CI, 1.3-7.1) among participants who had smoked 45 to 59 pack-years compared with never-smokers. Assuming that the multivariable-adjusted hazard ratios represent biologically causal associations between smoking status and risk of pancreatitis, we estimated that approximately 46% of cases of pancreatitis were attributable to smoking in this cohort.

We repeated the analyses stratifying by amount of alcohol intake: participants who in each examination reported drinking maximally 2 drinks per day for women and 3 drinks per day for men were categorized as consistent light to moderate drinkers, and participants who in at least 1 examination reported drinking above these limits were categorized as heavy drinkers. Most of the cases occurred among the consistent light to moderate drinkers (162 of 235 cases totally). Among these, hazard ratios were 1.6 (95% CI, 0.9-2.6), 1.5 (95% CI, 0.9-

**Table 4. Risk of Acute, Chronic, and Total Pancreatitis by Updated Information on Pack-Years of Smoking (Smoking Duration Among Ex-smokers) in Men and Women Combined<sup>a</sup>**

	Total No. of Cases	Adjusted Hazard Ratio (95% CI) <sup>b</sup>		
		Acute Pancreatitis	Chronic Pancreatitis	Total Pancreatitis
Never smokers	26	1.0	1.0	1.0
Current smokers, pack-years				
<15	21	1.3 (0.7-2.7)	1.1 (0.4-2.6)	1.4 (0.8-2.4)
15-29	38	2.2 (1.2-3.8)	1.2 (0.5-2.6)	1.7 (1.0-2.8)
30-44	43	2.8 (1.6-5.1)	2.3 (1.1-4.8)	2.5 (1.5-4.2)
45-59	27	3.2 (1.6-6.2)	3.1 (1.3-7.1)	3.2 (1.8-5.7)
≥60	23	2.9 (1.4-6.3)	4.1 (1.8-9.7)	3.7 (2.0-6.8)
Ex-smokers, No. of years smoked				
<30	23	2.0 (1.1-3.7)	0.8 (0.3-2.3)	1.5 (0.9-2.7)
≥30	27	2.7 (1.5-5.1)	1.1 (0.4-3.2)	2.2 (1.3-3.9)

Abbreviation: CI, confidence interval.

<sup>a</sup>Results from Cox proportional hazards regression analysis with age as the underlying time scale.

<sup>b</sup>Adjusted for sex, education level (<8 years, 8-11 years, >11 years), body mass index (calculated as weight in kilograms divided by height in meters squared; <20, 20-24.9, ≥25), and alcohol intake (continuous). Seven cases were excluded because of missing data on duration of smoking.

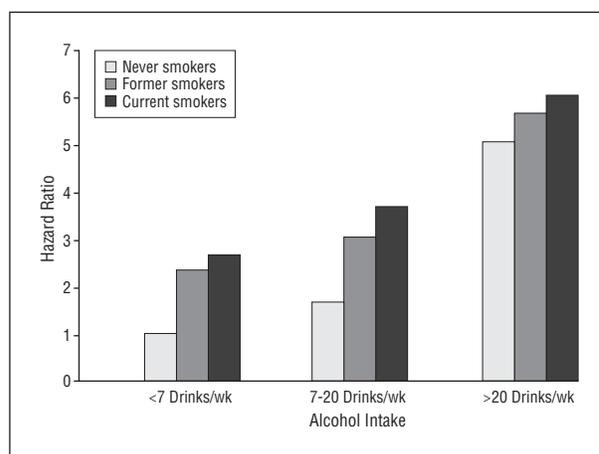
2.4), 2.3 (95% CI, 1.4-3.8), and 2.9 (95% CI, 1.5-5.8) in ex-smokers and current smokers of 1 to 14, 15 to 24, and 25 g/d or more of tobacco, respectively. Corresponding hazard ratios among the heavy drinkers were 1.7 (95% CI, 0.5-5.2), 1.4 (95% CI, 0.5-4.6), 2.4 (95% CI, 0.8-6.8), and 3.3 (95% CI, 1.1-10).

Incidence rates for total pancreatitis by smoking and alcohol are shown in the **Figure**. Within each category of alcohol intake, the incidence rate was higher among ex-smokers and current smokers compared with never-smokers. We found no evidence of interaction between alcohol intake and smoking on the risk of pancreatitis ( $P = .70$ ).

#### GALLSTONES AS A POTENTIAL MEDIATOR OF THE ASSOCIATION BETWEEN SMOKING AND PANCREATITIS

We performed analyses of gallstones as a potential mediator of the association between smoking and risk of pancreatitis. In total, 562 women and 251 men had gallstones before the end of follow-up. As expected, gallstones were associated with subsequent risk of pancreatitis (adjusted hazard ratio for total pancreatitis, 1.1; 95% CI, 0.7-1.5). However, adjusting for gallstones had little influence on our results, indicating that gallstone disease does not mediate the association between smoking and pancreatitis. For example, the adjusted hazard ratio of total pancreatitis among participants who smoked 15 to 24 g/d of tobacco was 2.5 (95% CI, 1.5-3.9) (Table 3) and 2.3 (95% CI, 1.5-3.7) after further adjustment for gallstones. In separate analyses of acute and chronic pancreatitis, including gallstones in the model did not affect our results.

To see if smoking is associated with increased risk of gallstone-associated pancreatitis, we performed exploratory analyses restricted to participants who had gallstones before or concomitant with pancreatitis diagnosis. This accounted for 831 participants of whom 65 developed pancreatitis during follow-up. In this subgroup, the adjusted hazard ratio of total pancreatitis was 1.4 (95% CI, 0.7-2.7) among ex-smokers and smokers of 1 to 14 g/d of tobacco combined and was 0.9 (95% CI,



**Figure.** Hazard ratios of pancreatitis by smoking status and weekly alcohol intake in men and women combined. Hazard ratios are adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and education level. One drink corresponds to 12 g of pure alcohol. The  $P$  value for interaction as estimated from the nested log-likelihood test was .70.

0.4-2.1) among smokers of 15 g/d of tobacco or more. Lastly, analyses were performed on participants free of gallstone disease and who were consistent light to moderate drinkers (idiopathic pancreatitis). In this subgroup, results were similar to main results.

#### COMMENT

In this large population-based study with long follow-up, we found that participants who at baseline reported smoking or being previous smokers had higher risks of developing acute and chronic pancreatitis compared with nonsmokers. We found comparable effect sizes in women and men and for acute and chronic pancreatitis. Furthermore, results strongly indicate that associations are independent of alcohol intake and of gallstone disease, which are risk factors considered to account for most cases of pancreatitis.

Most previous studies on smoking and pancreatitis find an increased risk among smokers; however, 2 case-control studies<sup>31,32</sup> did not observe an increased risk, but these studies included only individuals with alcohol use disorders (ie, persons with a heavy alcohol intake and thus a high risk of pancreatitis). Hence, relative risk estimates of pancreatitis according to smoking may be smaller than for individuals with a lower alcohol intake. Only 2 of the 4 studies<sup>12,18</sup> in which women are included found an increased risk of pancreatitis according to smoking in women, and 1 of these studies<sup>12</sup> found only a weak association. In the present study, we observed similar risks in men and women. Recently, Lindkvist et al<sup>11</sup> found an increased relative risk of 2.14 for developing acute pancreatitis in current smokers in a prospective cohort study. In that study, a dose-response effect was also observed after controlling for alcohol intake, whereas no adjustment for gallstone disease was performed. We did not observe an increased risk of pancreatitis according to smoking among participants with preceding or concomitant gallstone disease. This finding is in accordance with results of a study<sup>18</sup> that found that smoking was only associated with alcohol-associated and idiopathic pancreatitis, which also agrees with our findings.

The risk of total pancreatitis in ex-smokers was of similar size to the risk among light current smokers (1-14 g/d of tobacco). This relatively high risk in the ex-smokers did not seem to be attributable to sick-quitters because omitting 2 and 4 years of follow-up, respectively, had only limited effect on the size of the hazard ratio. Lung function (as measured by FEV<sub>1</sub>) within smoking categories ranged in the expected order (decreasing in the order of never-smokers, ex-smokers, and current smokers of 1-14, 15-24, and >25 g/d of tobacco, respectively). This finding further indicates that there was not a high proportion of sick-quitters among the ex-smokers. Also, the amount of carbon dioxide in expired air was similar among never-smokers and ex-smokers, which indicates that there was not a substantial fraction of current smokers who were misclassified as ex-smokers.

A high proportion of participants were smokers in this study cohort. A total of 62% were current smokers at their first enrollment in the CCHS, and we found that approximately 46% of the cases of pancreatitis in this cohort could be attributed to smoking. Currently, the proportion of smokers in the Danish population, as in most Western populations, has decreased to approximately 30%, and never-smokers and ex-smokers account for approximately 39% and 31%, respectively.<sup>33</sup>

This study has the advantages of a prospective design, large size, and complete follow-up information on all participants. A limitation of the study is that the diagnoses of acute and chronic pancreatitis in the Danish Hospital Discharge Register have not been validated. Only hospital admissions are registered, and contacts to general practitioners are not included. Hence, it is likely that not all cases of pancreatitis occurring during the study period are categorized as such in this study. Also, some misclassification between the diagnoses of acute and chronic pancreatitis have probably occurred because the symptoms and diagnostic criteria of acute and chronic

pancreatitis are overlapping and the 2 diseases can co-exist.<sup>34</sup> Such misclassification would result in similar observed associations between smoking and risk of acute and chronic pancreatitis, whereas the results for the joint outcome of pancreatitis are valid. Furthermore, we did not have information on the cause of the pancreatitis, and risk factors for gallstone-related pancreatitis may not be the same as for alcohol-related or idiopathic pancreatitis.<sup>11,18</sup> We addressed this issue in exploratory analyses, defining gallstone-related pancreatitis as cases of pancreatitis with preceding or concomitant gallstone disease and idiopathic pancreatitis as cases of pancreatitis with no history of gallstone disease and heavy alcohol intake. We also observed in accordance with previous studies<sup>18</sup> that smoking does not seem to be associated with increased risk of gallstone-related pancreatitis.

We observed an 11-fold risk of pancreatitis among participants with gallstone disease. However, this result should be interpreted with caution because almost all patients with pancreatitis are examined by abdominal ultrasonography at hospitalization, and gallstones will be detected also in patients with pancreatitis of other causes with prevalent gallstones unrelated to the attack of pancreatitis. Hence, a part of the rather large relative risk of pancreatitis according to gallstones may be owing to detection bias.

Apart from the epidemiologic evidence of an association between smoking and development of acute and chronic pancreatitis, a biological effect of smoking seems plausible because both animal studies and human studies<sup>19-21,35,36</sup> have demonstrated changes of the pancreas and in pancreatic functioning after exposure to tobacco smoke.

In conclusion, we found that smoking was associated with an increased risk of acute and chronic pancreatitis in both men and women. The risk associated with smoking was independent of alcohol and gallstone disease, which are risk factors suggested to be the main causes of pancreatitis.

**Accepted for Publication:** October 19, 2008.

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**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by grants from the Danish National Board of Health and the Danish Medical Research Council.

**Role of the Sponsors:** The funding organizations did not have any role in either the design or conduct of the study or preparation, review, or approval of the manuscript.

**Additional Contributions:** We thank the participants of the CCHS for their time and cooperation.

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### Correction

**Errors in Text and Table 1.** In the Original Investigation titled “Smoking and Risk of Acute and Chronic Pancreatitis Among Women and Men: A Population-Based Cohort Study” by Tolstrup et al, published in the March 23, 2009, issue of the *Archives* (2009;169[6]:603-609), an error in terminology occurred in the text on pages 604, 605, and 608 and in Table 1 on page 605. The term “carbon dioxide” should have read “carbon monoxide.” Also, on page 607, the sentence “Incidence rates for total pancreatitis by smoking and alcohol are shown in the Figure.” should have read “Hazard ratios for total pancreatitis by smoking and alcohol are shown in the Figure.”