Smoking Is Underrecognized as a Risk Factor for Chronic Pancreatitis

Dhiraj Yadav^a Adam Slivka^a Stuart Sherman^c Robert H. Hawes^d Michelle A. Anderson^e
Frank R. Burton^f Randall E. Brand^g Michele D. Lewis^h Timothy B. Gardnerⁱ
Andres Gelrud^j James DiSario^k Stephen T. Amann^l John Baillie^m Christopher Lawrence^d
Michael O'Connell^a Albert B. Lowenfelsⁿ Peter A. Banks^o David C. Whitcomb^{a, b}
for the North American Pancreatic Study Group

Departments of ^aMedicine and ^bHuman Genetics, University of Pittsburgh, Pittsburgh, Pa., ^cDepartment of Medicine, Indiana University Medical Center, Indianapolis, Ind., ^dDigestive Disease Center, Medical University of South Carolina, Charleston, S.C., ^eUniversity of Michigan, Ann Arbor, Mich., ^fDepartment of Internal Medicine, St. Louis University School of Medicine, St. Louis, Mo., ^gDepartment of Medicine, Evanston Northwestern Healthcare, Chicago, Ill., ^hDivision of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Fla., ⁱDartmouth-Hitchcock Medical Center, Lebanon, N.H., ^jDepartment of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, ^kDepartment of Medicine, University of Utah Health Science Center, Salt Lake City, Utah, ^lNorth Mississippi Medical Center, Tupelo, Miss., ^mDepartment of Medicine, Duke University Medical Center, Durham, N.C., ⁿDepartment of Surgery, New York Medical College, Valhalla, N.Y., and ^oDivision of Gastroenterology, Brigham and Women's Hospital, Boston, Mass., USA

Key Words

Chronic pancreatitis · Smoking · Alcohol · Risk factor

Abstract

Background/Aims: Smoking is an established risk factor for chronic pancreatitis (CP). We sought to identify how often and in which CP patients physicians consider smoking to be a risk factor. **Methods:** We analyzed data on CP patients and controls prospectively enrolled from 19 US centers in the North American Pancreatitis Study-2. We noted each subject's self-reported smoking status and quantified the amount and duration of smoking. We noted whether the enrolling physician (gastroenterologist with specific interest in pancreatology) classified alcohol as the etiology for CP and selected smoking as a risk factor. **Results:** Among 382/535 (71.4%) CP patients who were self-reported ever smokers,

physicians cited smoking as a risk factor in only 173/382 (45.3%). Physicians cited smoking as a risk factor more often among current smokers, when classifying alcohol as CP etiology, and with higher amount and duration of smoking. We observed a wide variability in physician decision to cite smoking as a risk factor. Multivariable regression analysis however confirmed that the association of CP with smoking was independent of physician decision to cite smoking as a risk factor. **Conclusions:** Physicians often underrecognize smoking as a CP risk factor. Efforts are needed to raise awareness of the association between smoking and CP.

Copyright © 2011 S. Karger AG, Basel and IAP

This study was presented as a Poster of Distinction at the Digestive Disorders Week, May 2010, New Orleans, La., USA. Dr. Burton passed away on August 2, 2010.

Introduction

Chronic pancreatitis (CP) is an inflammatory disorder most commonly associated with alcohol consumption [1–9]. Since 1982 [10], smoking has been recognized as a risk factor for CP, particularly in alcohol-related CP compared with CP arising from other causes [9–14]. Smoking has been included in the classification systems proposed for CP [15, 16]. We previously reported stratified analyses of various drinking levels to demonstrate that the association between smoking and CP is independent of alcohol, is dose-dependent, and increases with the level of alcohol consumption [17]. Similar results have been reported in a large population-based study [18]. Smoking has been linked to the evolution from acute to CP [19] and progression of CP [20–22]. Moreover, smoking cessation after CP diagnosis may slow disease progression [23]. Therefore, recognition of smoking as a risk factor for CP provides an opportunity for counseling and smoking cessation as an intervention for primary and secondary prevention.

However, it is unclear how often and in which patients physicians consider smoking as a risk factor for CP. Using data from the North American Pancreatitis Study-2 (NAPS2) [24], we compared patient self-reported smoking status with the enrolling physician assessment of smoking as a risk factor for CP.

Material and Methods

NAPS2 Study

NAPS2 is the largest, multi-site molecular epidemiology study of pancreatitis to date in North America. In this study, 19 secondary and tertiary academic medical centers with pancreatology expertise prospectively enrolled 1,000 pancreatitis patients (540 CP, 460 recurrent acute pancreatitis) and 595 control subjects between 2000 and 2006 [24]. Another center with primary care practice enrolled an additional 100 control subjects [24]. CP was diagnosed by definitive evidence on imaging studies (endoscopic retrograde cholangiopancreatography or abdominal computed tomography scan) (83%) or histology (5%). In 9% cases, the diagnosis was based on endoscopic ultrasound and/or magnetic resonance cholangiopancreatography. Control subjects were spouses (34.2%), family members (27.5%), or friends of affected individuals or were unrelated individuals (38.3%). The study was approved by the institutional review board at each participating center and all subjects provided informed consent prior to enrollment.

Self-Reported Smoking Status and Alcohol Consumption

Each patient and control subject provided information on whether he/she ever smoked (defined as >100 cigarettes during lifetime), date when starting smoking, date of quitting smoking (if applicable) and the average number of cigarettes smoked per

day [24]. Using this information, patients and control subjects were stratified into never or ever smokers. Ever smokers were further classified as past or current smokers. The amount of smoking was quantified as packs per day (<1 if a subject smoked <20 cigarettes/day or ≥ 1 if smoked ≥ 20 cigarettes/day), and the duration of smoking (years) and pack-years (average amount $\times$ duration) was determined for each individual. For this study, we analyzed data only from centers that enrolled CP patients. After excluding subjects with missing information on ever smoking status, the final sample size was 535 for CP patients and 591 for controls.

The information on self-reported alcohol consumption during the maximum lifetime drinking period was used to create five drinking categories as described previously [24]. The drinking categories were defined as: *Abstainer*: no alcohol use or <20 drinks in lifetime; *Light drinker*: ≤ 3 drinks/week; *Moderate drinker*: 4–7 drinks/week for females, 4–14 drinks/week for males; *Heavy drinker*: 8–34 drinks/week for females, 15–34 drinks/week for males, and *Very heavy drinker*: ≥ 35 drinks/week for either sex. One drink was defined as one beer, a glass of wine, one shot of liquor or a mixed drink. A high correlation between drinking categories and measure of *at-risk* drinking behavior (TWEAK score) was seen, as reported previously [17].

Diagnosis of Alcohol and Smoking by Physicians

The enrolling physicians were all board-certified gastroenterologist(s) with a specific interest in the diagnosis and management of pancreatic disorders. The enrolling physician was asked to select one or more diagnostic etiologies for CP from among the following choices: alcohol, idiopathic, hereditary, cystic fibrosis, pancreas divisum, hyperlipidemia, hypercalcemia, trauma, and other (with space provided to add details). Physicians were also provided a list of all known or potential risk factors for CP and asked to check off as many as they believed applied to the enrolled patient. Tobacco smoking was listed as one of the risk factors [24].

For each patient, we noted whether the enrolling physician classified alcohol as a diagnostic etiology or risk factor for CP and whether smoking was selected as a risk factor.

Data Analysis

Descriptive analyses are presented as proportions for categorical data and as mean $\pm$ SD or median and interquartile range for continuous data, as applicable. Bivariate comparisons for continuous variables were performed using the Mann-Whitney U test and for categorical data using the χ^2 test or Cochran-Armitage test, as applicable.

To evaluate whether the association between smoking and CP is independent of physician decision to cite smoking as a risk factor, we performed multivariable logistic regression analyses similar to our earlier publication [17] after stratification of the 13 centers (recruited 97% of all CP patients) into two groups based on whether physicians cited smoking as a risk factor in less or more than 50% of current smokers. In regression analyses, we used alcohol consumption (as drinking categories), age (as a continuous variable), sex (male, female), and current or maximum body mass index (normal/low, ≤ 25 ; overweight, >25 – ≤ 30 ; obese, >30) as covariates. Smoking was assessed as never or ever; never, past, current; never, <1, ≥ 1 PPD, and never, <12, 12–35, >35 pack-years. We used abstainers and light drinkers as the reference cat-

egory for alcohol consumption. Regression models were evaluated by the goodness-of-fit χ^2 test. Two-sided p values <0.05 were considered significant. Data analysis was performed using the R Project software (www.r-project.org) and SPSS version 16 (SPSS Inc., Chicago, Ill., USA).

Results

Prevalence of Smoking in the NAPS2 Cohort

As previously published [17], ever smoking was self-reported by 382 of the 535 CP patients enrolled (71.4%). Overall, 129 (24.1%) were past, and 253 (47.3%) were current smokers; 147 (28.7%) reported smoking <1 PPD, and 213 (41.5%) reported smoking $\geq$ 1 PPD. The prevalence of smoking was higher in men (ever, 80.4%; current, 53.9%; $\geq$ 1 PPD, 52.4%) compared with women (ever, 61.6%; current, 40%; $\geq$ 1 PPD, 29.5; $p < 0.001$ all comparisons).

Physician Classification of Smoking as a Risk Factor

Physicians cited tobacco smoking to be a risk factor in only 173 of the 382 patients who reported ever smoking (45.3%). Physicians were more likely to cite smoking as a risk factor in current compared with past smokers (53 vs. 30.2%, $p < 0.001$) (table 1). They were more likely to cite smoking as a risk factor among patients reporting higher duration (median 32.5 vs. 26.4 years, $p < 0.001$) and amount (30.6 vs. 22.1 pack-years, $p = 0.003$) of smoking.

Physician Classification of Smoking as a Risk Factor after Stratification by Alcohol Etiology

Overall, physicians considered alcohol as a diagnostic etiology and/or risk factor in 238 of the 535 CP patients (44.7%) in the NAPS2 cohort. Among smokers, physicians were more likely to cite tobacco smoking as risk factor among patients in whom they also considered alcohol as an etiologic diagnosis compared with CP patients with non-alcohol etiologies (54.5 vs. 32.5%, $p < 0.001$). They cited smoking as a risk factor equally among past and current smokers (51.1 vs. 55.4%, $p = 0.62$) in conjunction with an alcohol diagnosis. However, among patients for whom alcohol was not cited as a diagnostic etiology, physicians cited smoking as a risk factor more often among current compared with past smokers (47.4 vs. 19%, $p < 0.001$). Among current smokers, physicians were equally likely to cite smoking as a risk factor, irrespective of alcohol diagnosis (55.4 vs. 47.4%, $p = 0.27$) (table 1).

In the alcohol etiology group, neither duration (median 32.5 vs. 31.8 years, $p = 0.76$) nor amount (30.4 vs. 25.6 pack-years, $p = 0.19$) of smoking affected whether physi-

Table 1. Self-reported smoking status compared with whether the enrolling physician cited smoking as a risk factor in CP in the NAPS2 cohort

Patient group	Number	Number (%) in whom physician cited smoking as a risk factor for CP
Ever smoked (all)	382	173 (45.3)
Alcohol etiology	222	121 (54.5)
No alcohol etiology	160	52 (32.5)
Current smokers (all)	253	134 (53.0)
Alcohol etiology	177	98 (55.4)
No alcohol etiology	76	36 (47.4)
Past smokers (all)	129	39 (30.2)
Alcohol etiology	45	23 (51.1)
No alcohol etiology	84	16 (19.0)
One or more packs/day	213	106 (49.8)
Alcohol etiology	127	74 (58.3)
Non-alcohol etiology	86	32 (37.2)
Less than one pack/day	147	58 (39.5)
Alcohol etiology	85	42 (49.4)
No alcohol etiology	62	16 (25.8)

All patients: $p < 0.001$ (alcohol vs. no alcohol etiology); $p < 0.001$ (current vs. past smokers).

No alcohol etiology: $p < 0.001$ (current vs. past smokers).

Alcohol etiology vs. no alcohol etiology: $p < 0.001$ (past smokers); $p = 0.006$ (less than one pack/day); $p = 0.003$ (one or more packs/day).

The number of patients in the smoking categories (current; past; packs/day) do not equal to ever smokers due to missing information.

cians cited smoking as a risk factor. The results in the alcohol etiology group were similar when data were evaluated after stratification by current or past smoking status or as packs per day (data not shown).

Among patients not diagnosed with an alcohol etiology, both the duration [median 35.0 (interquartile range 21.7, 40.3) vs. 22.3 (10.1, 31.7) years, $p < 0.001$] and amount [median 31.7 (17.4, 44.6) vs. 17.3 (4.9, 35.6) pack-years, $p = 0.009$] of smoking were greater for subjects in whom physicians cited smoking to be a risk factor.

Self-Reported Smoking Status and Physician Classification after Stratification by Center

The prevalence of self-reported smoking by CP patients at the 13 centers that enrolled 97% cases was generally similar (fig. 1). However, wide variability was seen in the smoking classification by physicians at these centers (fig. 2a, b). The proportion of patients in whom physicians cited smoking as a risk factor ranged from as low as

Fig. 1. Distribution by enrolling center of self-reported smoking status in the NAPS2 cohort.

Fig. 2. Physician classification of smoking as a risk factor for CP among (a) self-reported past or current smokers, and (b) by self-reported amount of smoking in the NAPS2 cohort.

Table 2. Multivariable logistic regression analyses showing association between smoking with CP in the NAPS2 study after stratification of centers based on whether physicians cited smoking as a risk factor

Smoking status	Centers where physicians cited smoking as a CP risk factor in			
	≤50% current smokers		>50% current smokers	
	odds ratio (95% CI)	p value	odds ratio (95% CI)	p value
Past smoker	1.52 (0.87–2.63)	0.14	1.64 (0.97–2.79)	0.07
Current smoker	3.08 (1.83–5.17)	<0.001	2.43 (1.49–3.96)	<0.001
<1 pack/day	2.12 (1.25–3.62)	0.006	1.57 (0.94–2.64)	0.09
≥1 packs/day	2.52 (1.45–4.36)	0.001	2.47 (1.48–4.10)	<0.001
<12 pack-years	1.55 (0.86–2.81)	0.15	1.32 (0.70–2.47)	0.40
12–35 pack-years	2.68 (1.46–4.93)	0.002	2.11 (1.21–3.67)	0.009
>35 pack-years	4.15 (2.05–8.39)	<0.001	4.47 (2.25–8.88)	<0.001

Reference category for each comparison is ‘never smoker’. Models shown are also adjusted for age, sex, alcohol consumption (drinking categories), and body mass index.

Sample size: centers where smoking was cited as a risk factor: in ≤50% current smokers: controls – 271; CP – 282; in >50% current smokers: controls – 310; CP – 243.

Effective sample sizes for comparisons ranged from 79 to 88% for controls, and from 70 to 93% for CP patients.

0% for past smokers, 8.3% for current smokers, and 29% for patients who smoked ≥1 packs/day to as high as 100% for each of these categories (fig. 2a, b).

Table 2 shows data on multivariable logistic regression analyses for the association between smoking and CP after stratification of the enrolling centers based on whether physicians cited smoking as a risk factor for CP in less or more than 50% of self-reported current smokers. An independent association between smoking and CP was seen in both strata, and the strength of association between smoking and CP was similar irrespective of physician’s consideration of smoking as a risk factor. When the center was used as a covariate in the regression models, it was not significant, while the association between smoking and CP remained significant (data not shown).

Stratified Analyses by Sex

Physician citation of smoking as a risk factor was generally similar overall and for alcohol diagnosis when stratified by sex for all comparisons (data not shown).

Discussion

Although more than two-thirds of patients with CP in our cohort reported smoking cigarettes, physicians – all of whom should be quite familiar with CP as a disease – cited smoking as a risk factor less than half the time. Phy-

sicians were more likely to cite smoking as a risk factor among current smokers, among patients reporting higher level of smoking, and with a concurrent alcohol diagnosis. As expected, the association between smoking and CP was independent of the physician’s decision to cite smoking as a risk factor.

Such underappreciation of the association between smoking and CP varied widely among individual physicians. Possible reasons for this striking variability could be a belief of physicians that the association between smoking and CP is confounded by alcohol, evidence too unconvincing for physicians to acknowledge this association, or a lack of awareness of the association between smoking and CP. It is therefore possible that while being aware of the smoking status of the patients, physicians did not consider it to be a risk factor.

We examined the distribution of self-reported smoking at the participating centers to determine whether this variability could be explained by differences in the prevalence of smoking. However, the prevalence of smoking was generally similar across the participating centers. Furthermore, on regression analyses, a strong dose-dependent association of smoking with CP was seen after controlling for alcohol consumption, age, sex, and body mass index. A similar association of smoking with CP after stratification of the centers indicates that this association is independent of physician classification.

Strong epidemiologic evidence in case-control as well as population-based studies has long demonstrated an association between smoking with CP [9–14, 17, 18] and, more recently, with acute pancreatitis [25]. The association between smoking and CP is stronger among patients who also consume alcohol [26]. However, two recent studies, including our own, have demonstrated that the association between smoking and CP is independent of alcohol [17, 18], increased with the amount of consumption, and is possibly synergistic with alcohol [17]. A recent population-based study identified the attributable risk associated with smoking for pancreatitis to be 46% [18]. Clinical data also support associations between smoking and CP risk and progression [19–23]. Thus, the available evidence points toward a strong role for smoking in the development and progression of CP.

Physician advice and counseling has been shown to increase tobacco cessation rates. Even a simple advice affects cessation rates and the benefit increases with intensive intervention and reinforcements on follow-up visits [27]. We therefore urge greater awareness of the association between smoking and CP to ensure physicians inquire about smoking status among pancreatitis patients and further emphasize and encourage smoking cessation among patients who smoke. In addition to preventing disease progression, tobacco cessation in these patients may also help in reducing the effects of other tobacco-related diseases, the prevalence of which is high in patients with CP [28]. In addition to gastroenterologists, our findings are specifically relevant to all internists and primary care physicians who follow these patients longitudinally and see them more frequently than specialists.

A potential limitation of our study is the choice of controls. Spouses, family members and friends used as controls in our study may have shared smoking habits with the patients. However, a higher rate of smoking in controls would only result in a 'conservative bias' by lowering the odds ratio for the association between smoking and

CP. Moreover, the choice of controls would not be expected to influence the decision of enrolling physician whether to cite smoking as a CP risk factor. Secondly, other than alcohol etiology, we do not know what factors influenced physician decision to cite smoking as a risk factor for CP.

In conclusion, cigarette smoking is common in CP patients. However, physicians often underappreciate the influence of smoking on the development and progression of CP. Efforts are needed to raise physician and public awareness of the association between smoking and CP and toward increasing use of smoking cessation treatment for primary and secondary prevention.

Acknowledgments

This research was supported by National Institutes of Health (NIDDK) DK061451 (D.C.W.), the National Pancreas Foundation (D.C.W.), Robert and Vicki Hall, and Andrew and Michelle Aloe. Dr. Lowenfels is supported in part by Solvay Pharmaceuticals and CD Smithers Foundation.

The following physicians and centers also contributed patients to this study: Mary E. Money, Washington County Hospital, Hagerstown, Md.; Joseph Romagnuolo, MD, Peter B. Cotton, MD, Digestive Disease Center, Medical University of South Carolina, Charleston, S.C.; Simon K. Lo, MD, Department of Medicine, Cedars-Sinai Medical Center, University of California, Los Angeles, Calif.; Mark T. DeMeo, MD, Department of Medicine, Rush University Medical Center, Chicago, Ill.; William M. Steinberg, MD, Washington Hospital Center, Washington, D.C.; Michael L. Kochman, MD, Department of Medicine, University of Pennsylvania, Philadelphia, Pa.; Babak Etemad, MD, Department of Gastroenterology and Hepatology, Ochsner Medical Center, New Orleans, La.; Christopher E. Forsmark, MD, Department of Medicine, University of Florida, Gainesville, Fla., USA.

The authors thank the following individuals from the Department of Medicine, University of Pittsburgh, Pittsburgh, Pa.: Michelle L. Kienholz for editorial assistance, Beth Elinoff, RN, MPH for help in patient recruitment, Emil Bauer and Pat Schuetz for data entry and data management, and Elizabeth D. Kennard, PhD, Epidemiology Data Center, University of Pittsburgh, Pa., for reviewing the manuscript and assisting with the statistical analyses.

References

- 1 Ammann RW, Akovbiantz A, Largiader F, Schueler G: Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology* 1984;86:820–828.
- 2 Andersen BN, Pedersen NT, Scheel J, Worning H: Incidence of alcoholic chronic pancreatitis in Copenhagen. *Scand J Gastroenterol* 1982;17:247–252.
- 3 Dite P, Stary K, Novotny I, Precechtelova M, Dolina J, Lata J, Zboril V: Incidence of chronic pancreatitis in the Czech Republic. *Eur J Gastroenterol Hepatol* 2001;13:749–750.
- 4 Durbec JP, Sarles H: Multicenter survey of the etiology of pancreatic diseases. Relationship between the relative risk of developing chronic pancreatitis and alcohol, protein and lipid consumption. *Digestion* 1978;18:337–350.
- 5 Gastard J, Joubaud F, Farbos T, Loussouarn J, Marion J, Pannier M, Renaudet F, Valdazo R, Gosselin M: Etiology and course of primary chronic pancreatitis in western France. *Digestion* 1973;9:416–428.
- 6 Lankisch PG, Assmus C, Maisonneuve P, Lowenfels AB: Epidemiology of pancreatic diseases in Luneburg County. A study in a defined German population. *Pancreatol* 2002;2:469–477.

- 7 Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP: The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994;107:1481–1487.
- 8 Robles-Diaz G, Vargas F, Uscanga L, Fernandez-del Castillo C: Chronic pancreatitis in Mexico City. *Pancreas* 1990;5:479–483.
- 9 Talamini G, Bassi C, Falconi M, Sartori N, Salvia R, Rigo L, Castagnini A, Di Francesco V, Frulloni L, Bovo P, Vaona B, Angelini G, Vantini I, Cavallini G, Pederzoli P: Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. *Dig Dis Sci* 1999;44:1303–1311.
- 10 Yen S, Hsieh CC, MacMahon B: Consumption of alcohol and tobacco and other risk factors for pancreatitis. *Am J Epidemiol* 1982;116:407–414.
- 11 Bourliere M, Barthet M, Berthezene P, Durbec JP, Sarles H: Is tobacco a risk factor for chronic pancreatitis and alcoholic cirrhosis? *Gut* 1991;32:1392–1395.
- 12 Lin Y, Tamakoshi A, Hayakawa T, Ogawa M, Ohno Y: Cigarette smoking as a risk factor for chronic pancreatitis: a case-control study in Japan. *Research Committee on Intractable Pancreatic Diseases. Pancreas* 2000;21:109–114.
- 13 Lowenfels AB, Zwemer FL, Jhangiani S, Pitchumoni CS: Pancreatitis in a native American Indian population. *Pancreas* 1987;2:694–697.
- 14 Morton C, Klatsky AL, Udaltsova N: Smoking, coffee, and pancreatitis. *Am J Gastroenterol* 2004;99:731–738.
- 15 Etemad B, Whitcomb DC: Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;120:682–707.
- 16 Schneider A, Lohr JM, Singer MV: The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007;42:101–119.
- 17 Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J, Sherman S, DiSario J, Burton FR, Gardner TB, Amann ST, Gelrud A, Lawrence C, Elinoff B, Greer JB, O'Connell M, Barmada MM, Slivka A, Whitcomb DC: Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med* 2009;169:1035–1045.
- 18 Tolstrup JS, Kristiansen L, Becker U, Gronbaek M: Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. *Arch Intern Med* 2009;169:603–609.
- 19 Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P: Natural history of acute pancreatitis: a long-term population-based study. *Am J Gastroenterol* 2009;104:2797–2806.
- 20 Imoto M, DiMagno EP: Cigarette smoking increases the risk of pancreatic calcification in late-onset but not early-onset idiopathic chronic pancreatitis. *Pancreas* 2000;21:115–119.
- 21 Maisonneuve P, Frulloni L, Mullhaupt B, Faitini K, Cavallini G, Lowenfels AB, Ammann RW: Impact of smoking on patients with idiopathic chronic pancreatitis. *Pancreas* 2006;33:163–168.
- 22 Maisonneuve P, Lowenfels AB, Mullhaupt B, Cavallini G, Lankisch PG, Andersen JR, DiMagno EP, Andren-Sandberg A, Domellof L, Frulloni L, Ammann RW: Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. *Gut* 2005;54:510–514.
- 23 Talamini G, Bassi C, Falconi M, Sartori N, Vaona B, Bovo P, Benini L, Cavallini G, Pederzoli P, Vantini I: Smoking cessation at the clinical onset of chronic pancreatitis and risk of pancreatic calcifications. *Pancreas* 2007;35:320–326.
- 24 Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J, Sherman S, Disario J, Burton FR, Gardner TB, Amann ST, Gelrud A, Lo SK, Demeo MT, Steinberg WM, Kochman ML, Etemad B, Forsmark CE, Elinoff B, Greer JB, O'Connell M, Lamb J, Barmada MM: Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study-2 (NAPS2). *Pancreatol* 2008;8:520–531.
- 25 Lindkvist B, Appelros S, Manjer J, Berglund G, Borgstrom A: A prospective cohort study of smoking in acute pancreatitis. *Pancreatol* 2008;8:63–70.
- 26 Falk DE YH, Hiller-Sturmhofel S: An Epidemiological analysis of co-occurring alcohol and tobacco use and disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Alcohol Res Health* 2006;29:162–171.
- 27 Stead LF, Bergson G, Lancaster T: Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2008;CD000165.
- 28 Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, DiMagno EP, Andren-Sandberg A, Domellof L, Di Francesco V: Prognosis of chronic pancreatitis: an international multicenter study. *International Pancreatitis Study Group. Am J Gastroenterol* 1994;89:1467–1471.