4. Chronic Pancreatitis and Pancreatic Cancer, Lifestyle-Related Diseases

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Abstract

In Japan, the number of patients with both chronic pancreatitis (CP) and pancreatic cancer (PC) is increasing. A nationwide survey on CP revealed that the total number of patients treated for CP in Japan in 2002 was estimated as 45,200 (95% confidence interval, 35,600-54,700), and 20,137 patients died of PC in 2002. Alcoholic pancreatitis was the most common type of pancreatitis (67.5 %). Cigarette smoking was an independent and significant risk factor for CP. The risks of pancreatic and nonpancreatic cancers increased in the course of CP. While alcohol consumption may increase the risk of PC via CP, smoking was important as a risk factor for both CP and PC. The increasing incidence of PC was closely related to the increasing intake of animal fat. Lifestyle in patients with CP appeared to be the same as that in patients with PC. Environmental factors such as lifestyle in combination with genetic factors may increase the risk for both CP and PC. Therefore, changing and improving lifestyle habits such as drinking, smoking and nutrition may reduce the risks for both CP and PC.

Key words: chronic pancreatitis, pancreatic cancer, alcohol consumption, smoking, environmental factor

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Introduction

“Lifestyle-related diseases” are defined as those in which improvement of “lifestyle” such as dietary patterns, exercise, and smoking, and drinking habits reduces the risk of these diseases. Hence, we report the lifestyle which is a risk for chronic pancreatitis (CP) and pancreatic cancer (PC) based on epidemiological studies by the Research Committee of Intractable Pancreatic Diseases and on other published literatures.

Estimated Number of Patients With Chronic Pancreatitis

From a nationwide survey on CP in 2002, the total number of patients treated for CP in Japan in 2002 was estimated as 45,200 (95% confidence interval, CI;35,600-54,700) with an overall prevalence rate of 35.5 per 100,000 population (1). An estimated crude annual incidence rate was 14.4 per 100,000 population. The most common type of CP was alcoholic pancreatitis (67.5%), the second and the

third were idiopathic (20.6%) and gallstone-induced pancreatitis (3.1%), respectively. Compared with the last nationwide survey in 1999 (2), the estimated total number of patients treated for CP increased by approximately 7.6% during the last 3 years (42,000 in 1999). The overall prevalence rate of CP also increased by approximately 6.9% (35.5 per 100,000 population in 1999). On the other hand, an estimated crude annual incidence rate showed more than a 2-fold increase over the last survey (5.8 per 100,000 population in 1999).

Drinking Habits and Chronic Pancreatitis

Compared with the findings in the last survey in 1999, the proportion of patients with alcoholic pancreatitis has increased greatly, from 54.0% to 67.5%, whereas that of idiopathic CP has decreased from 30.0% to 20.6% (1, 2). Improved diagnostic accuracy, associated with the widespread use of advanced techniques such as computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) might have decreased the incidence of idiopathic CP. A significant dose-response relationship was observed

Table 1. Number of Patients with Chronic Pancreatitis Who Died of Malignant Diseases during Follow Up Periods for 8 Years

Organ	No. of Patients
Pancreas	27 (2)
Lung	16 (2)
Liver	14
Colon	12 (2)
Esophagus	11 (2)
Stomach	9 (3)
Bile duct	9 (1)
Pharynx/Larynx	6 (1)
Leukemia	4
Malignant Lymphoma	3
Prostate	2
Miscellaneous	4 (6)
Total	117 (19)

() : Number of patients died of other cancers

between daily ethanol intake and the risk of CP (3). The increasing incidence of CP in recent years (crude annual incidence rate per 100,000 population; 2.0 in 1974, 5.0-5.9 in 1992-1993, 5.4 in 1994, 5.8 in 1999, and 14.4 in 2002) may be closely related to the gradually increasing alcohol consumption in Japan. The estimated number of drinkers was 66,931,000 people in 1999, and the consumed amount of alcohol in Japan was 832,524 kL overall, which is equivalent to 8.3 L per one adult person. The number of heavy drinkers who consume more than 150 g ethanol per a day is also increasing (<http://www.ncc.go.jp/jp/statistics/2003/index.html>). These increases in alcohol consumption and heavy drinkers could explain the increase in the patients with alcoholic pancreatitis. Figure 1 clearly indicates that the number of patients with CP increase 10-20 years after the increase in the number of heavy drinkers.

Based on the epidemiological studies (the total estimated number of patients treated for CP was 45,200 and the proportion of patients with alcoholic pancreatitis was 67.5 % in Japan), the number of patients with alcoholic pancreatitis was calculated as 30,284. Hence, the proportion of patients with alcoholic pancreatitis (30,284 patients) in heavy drinkers (270,000 people) was calculated as approximately 1.3%. To confirm the incidence of alcoholic pancreatitis in heavy drinkers, we conducted a questionnaire survey for male members who belong to Zen-Nippon Danshu Renmei (all-Japan Sobriety Association). Of 7,876 members to whom the questionnaire was mailed, 4,120 people replied (response rate, 52.3%). Of 4,120, 857 people (20.8%) had been previously diagnosed as pancreatitis: alcoholic 10.1%, biliary 0.8%, and idiopathic 9.9% (4). A history of heavy drinking was confirmed in 373 of 418 people who had been diag-

nosed as alcoholic pancreatitis and 345 of 407 people who had been diagnosed as idiopathic pancreatitis. We assumed therefore that these people had suffered from alcoholic pancreatitis, and estimated that the incidence of alcoholic pancreatitis in heavy drinkers is 17.4% (4). Thus the incidence of alcoholic pancreatitis in heavy drinkers might be much higher than the estimated incidence of 1.3%. The mean age ($\pm$ SD) of these heavy drinkers who had been diagnosed as alcoholic pancreatitis was 43.0 ($\pm$ 10.5). Heavy drinkers who had a history of alcoholic pancreatitis began drinking significantly younger (19.1 ± 3.9 vs. 19.5 ± 4.6 years old, $P < 0.05$) and consumed a larger amount of ethanol (converted to Japanese sake; $1,314 \pm 954$ vs. $1,224 \pm 846$ ml, $P < 0.05$) compared with those without a history of pancreatitis.

Smoking and Chronic Pancreatitis

In Japan, 43.3% of males and 10.2% of females (24.0% of total) over age 20 smoke according to statistics compiled by the Japanese Government (<http://www.mhlw.go.jp/topics/tobacco/toukei/kituen.html>). Of 957 patients with CP 63.3% were smokers. In particular, 78.2% of alcoholic CP was smokers (Fig. 2). After adjusting for body mass index (BMI), education level, and alcohol consumption, the odds ratios (ORs) [and their 95% confidence intervals (CIs)] were 7.8 (2.2-27.3) for all current smokers, and 14.7 (3.1-69.9), 5.5 (1.5-20.1), and 12.2 (2.4-71.0) for current smokers who consumed < 20, 20-39, and ≥ 40 cigarettes per day, respectively (5). Risk of CP significantly increased with increasing cumulative amount measured as cigarette-years, although the correlation was not found between daily cigarette consumption and OR for CP. Compared with current smokers, ex-smokers were at a decreased risk of CP (OR=1.7, 95% CI=0.4-6.3). Nicotine is known to inhibit pancreatic exocrine secretion via the release of catecholamine (6). In addition, heavy smokers appear to develop pancreatic calcification earlier and, to some degree, more often than non-smokers (7). Several previous studies have indicated that smoking is a significant risk factor for CP independent of drinking (5, 8).

Chronic Pancreatitis and Pancreatic Cancer

Lowenfels et al (9) performed a multicenter historical cohort study of 2,015 patients with CP recruited from six countries and identified a total of 56 patients with PC (2.8 %) during a mean follow-up of 7.4 ± 6.2 years. The expected number of PC calculated from country-specific incidence data and adjusted for age and sex was 2.1, yielding a standardized incidence ratio (SIR) of 26.3 (95% CI, 19.9-34.2). Even if only patients with a follow-up of longer than five years were considered, the number of PC found was larger than expected (SIR; 18.0 vs. 1.25) (9). In a population-based study of 7,956 individuals, Ekblom et al (10) found a SIR of 3.8 among patients with CP. Talamini et al (11) performed a longitudinal study in 715 patients with

Figure 1. Relationship between estimated number of heavy drinkers and estimated prevalence rate of chronic pancreatitis per 100,000 population.

Figure 2. Incidence of smokers in 957 patients with chronic pancreatitis (A) and 648 patients with alcoholic chronic pancreatitis (B).

CP for more than 10 years and found an increased risk of PC (SIR;18.5). Consistent with these observations, we found development of PC in 29 of 964 patients with CP (3.0%) during a longitudinal study over 8 years (12) (Table 1). An excess relative risk of 5.0 (95% CI, 1.0-14.6) has also been found in tropical calcifying pancreatitis, independent of alcohol or smoking (13). Recent studies in hereditary pancreatitis revealed that the estimated cumulative risk of PC to age 70 years in patients with hereditary pancreatitis approaches 40% (14). For patients with a paternal inheritance pattern, the cumulative risk of pancreatic cancer is approximately 75% (14). Taken together, these findings indicate that the risk of PC is significantly high in patients with CP. CP has to be considered a risk factor for PC or a precursor of PC.

Smoking and Pancreatic Cancer

Cigarette smoking has been modestly associated with risk of pancreatic cancer and is estimated to account for between 25% and 29% of pancreatic cancer incidence (15). During a mean ($\pm$ SD) follow-up of 8.1 ($\pm$ 1.8) years of 110,792

Figure 3. Effects of alcohol and smoking on the development of chronic pancreatitis and pancreatic cancer.

Japanese inhabitants, aged 40-79 years, 225 deaths due to PC were identified. After adjustment for age, body mass index, history of diabetes mellitus, and gallbladder diseases, the relative risks (RRs) of PC for current smokers were 1.6 (95% CI, 0.95-2.6) in males, and 1.7 (95% CI, 0.84-3.3) in females (16). Men who smoked more than 40 cigarettes per day had a substantially higher risk of PC, with a RR of 3.3 (95% CI, 1.4-8.1). A significantly decreasing trend in risk with increasing years after smoking cessation was observed among male ex-smokers; the RR was 0.85 (95% CI, 0.36-2.0) for those who had quit smoking for ≥ 20 years (16). Bonelli et al (17) reported that current smokers in a case-control study were at increased risk for PC (OR=2.36; 95% CI, 1.53-3.63) and the magnitude of the risk was related to the lifetime amount of smoking. After 15 years from cessation of smoking, the risk for PC among former smokers dropped to the level of a lifetime non-smoker regardless of the total amount of smoking. Fuchs et al (18) have also reported that, compared with participants who continued to smoke, former smokers had a 48% reduction in PC risk within 2 years of quitting and that the relative risk of PC among former smokers approached that for never smokers after less than 10 years of smoking cessation.

In contrast to smoking, regarding alcohol consumption, the daily amount, years of drinking and cumulative amount were not associated with increased risk of death from PC in either men or women (9, 19). Since, however, 78.2% of alcoholic CP patients are smokers in Japan (Fig. 2), and such a high number of smokers in alcoholic CP may mean that it is not possible to analyze drinking and smoking as independent risk factors for PC. CP is known to be a high risk factor for PC (9-14, and present study) and drinking habit is a well-known risk factor for CP (3,4, and present study). It is plausible therefore that alcohol consumption is a risk factor for PC via CP. On the other hand, smoking is a risk factor not only for CP but also for PC (Fig. 3).

Diet and PC

Although it is suggested that 30% of PC may be related to dietary food, it is not known how food affects the onset of PC (20). Since the pancreas is not directly exposed to ingested foods as the gastrointestinal tract, there are possibilities that alterations of metabolic status and metabolites or

Figure 4. Relationship between daily amount of fat intake and the number of patients who died of pancreatic cancer.

carcinogens in the blood have some influence on the pancreas. A previous case-control study showed that an excess of total energy intake increases the incidence of PC (21).

Recent meta-analysis of the available data in Western countries provided evidence that the risk of PC may increase slightly with increasing body mass index (BMI), and that obese individuals ($\text{BMI} \geq 30 \text{ kg/m}^2$) have a 19% higher risk for PC compared with those with a normal BMI (22 kg/m^2) (22, 23). However, no association between BMI and PC was observed in Japan, probably because the number of obese people in Japan is less than that in Western countries. Thus the results of epidemiological studies concerning an association between BMI and PC are still controversial.

Insulin resistance and abnormal glucose metabolism are possible explanations for the relationships between PC and obesity. Indeed, diabetes mellitus is a known risk factor for PC (17, 19, 24, 25) and physical exercise decreases the risk

for PC (23). Increases in BMI by excess food or energy intake are associated with an increase in risk of hyperinsulinemia and diabetes. In addition, an elevation of BMI may cause lipid peroxidation and DNA damage in the pancreas resulting in PC.

Epidemiological studies have also shown that the incidence of PC tends to increase in countries or regions where a larger amount of fat is taken, although the conclusion is still controversial in case-control studies. An increase in fat intake in Japanese is correlated with an increase in the number of PC patients after 10-20 years (Fig. 4). The epidemiological evidence relating to diets high in saturated or animal fat and the risk of PC is inconsistent. However, in an animal study, it is reported that intake of a high-saturated fat diet may cause pre-malignant lesions in the pancreas (20). In contrast, many studies have shown that high vegetable or fruit intake may have a protective effect against PC development (25).

Conclusions

Smoking and drinking are independent risk factors for CP. While drinking is a risk factor for CP and it is also a risk factor for PC via CP, smoking is a risk factor not only for CP but also for PC. Lifestyle in CP patients appears to be the same as that in PC patients. Environmental factors such as lifestyle in combination with genetic factors may increase the risk for both CP and PC. Therefore, changing and improving lifestyle such as drinking habits, smoking and nutrition may reduce the risk for CP and PC.

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