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Citation	Fukushima Journal of Medical Science. 63(1): 1-7
Issue Date	2017
URL	<a href="http://ir.fmu.ac.jp/dspace/handle/123456789/573">http://ir.fmu.ac.jp/dspace/handle/123456789/573</a>
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DOI	10.5387/fms.2016-14
Text Version	publisher

[Review]

## Early diagnosis of chronic pancreatitis : understanding the factors associated with the development of chronic pancreatitis

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(Received November 1, 2016, accepted March 14, 2017)

### Abstract

The prognosis of advanced chronic pancreatitis (CP) is poor with the mortality rate approximately two-fold higher than the general population according to a survey of the prognosis of CP. From this standpoint, the concept of early CP was propagated in Japan in 2009 to encourage the medical treatment for the earlier stages of CP. That is, picking up the patients suspicious for early CP and then providing medical treatment for them are very important not only for patients, but also for health care economics. In this review, we described some potential factors associated with the development of CP (alcohol, smoking, past history of acute pancreatitis, aging, gallstone, and gender) that are extremely important to discover patients with early-stage CP.

**Key words :** chronic pancreatitis, endoscopic ultrasound, risk factor

### Introduction

Understanding of the pathophysiology and therapy of chronic pancreatitis (CP) has innovatively advanced since Thomas Cawley first reported CP in 1,788<sup>1)</sup>. However, the prognosis of CP is poor with the mortality rate approximately two-fold higher than the general population according to a survey of the prognosis of CP. A worldwide epidemiological survey in 1,993 showed that the incidence rate of pancreatic cancer is as high as 26-fold of the age/sex/country-standardized predicted incidence<sup>2)</sup>. Therefore, cancer develops relatively frequently in CP but its diagnosis becomes difficult in advanced CP due to increased fibrosis and pancreatic calculi<sup>3)</sup>. Although it has been understood that early diagnosis and proper treatment of CP are extremely important, diagnosis has been difficult because the clinical features of early CP are unclear ; diagnostic imaging techniques capable of easily detecting minor pancreatic parenchyma/duct abnormalities have not been established. Even in the current clinical settings,

patients having abdominal symptoms or exhibiting abnormal functional testing results are frequently found to have advanced CP. However, the advance in endoscopic ultrasonography (EUS) in recent years has allowed less invasive examinations while precisely capturing slight changes in the so-called undetectable organ, casting light on the early stages of CP<sup>4-8)</sup>. Against such backdrop, the concept of early-stage CP was propagated in Japan in 2009 to encourage the medical treatment for the earlier stages of CP<sup>9)</sup> (Table 1, Fig. 1). In order to understand whether the disease that meets the criteria for early-stage CP actually progresses to advanced CP, prospective studies are needed. However, at present, picking up the patients suspicious for early CP and providing medical treatment for them are very important not only for patients, but also for health care economics. Here, we review potential factors associated with the development of CP that are extremely important to discover patients with early-stage CP.

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Table 1. Clinical diagnostic criteria for early chronic pancreatitis : More than two clinical signs+Imaging findings<sup>9)</sup>

<b>Clinical signs</b>	
1)	Repeated upper abdominal pain
2)	Abnormal pancreatic enzyme levels in the serum or urine
3)	Abnormal pancreatic exocrine function
4)	Continuous heavy drinking of alcohol equivalent to or more than 80 g/day of pure ethanol
<b>Imaging findings (Either a or b)</b>	
a.	More than two among the seven features including any of (1)-(4)
(1)	Lobularity with honeycombing
(2)	Lobularity without honeycombing
(3)	Hyperechoic foci without shadowing
(4)	Stranding
(5)	Cysts
(6)	Dilated side branches
(7)	Hyperechoic main pancreatic duct (MPD) margin
b.	Irregular dilatation of more than 3 duct branches on ERP

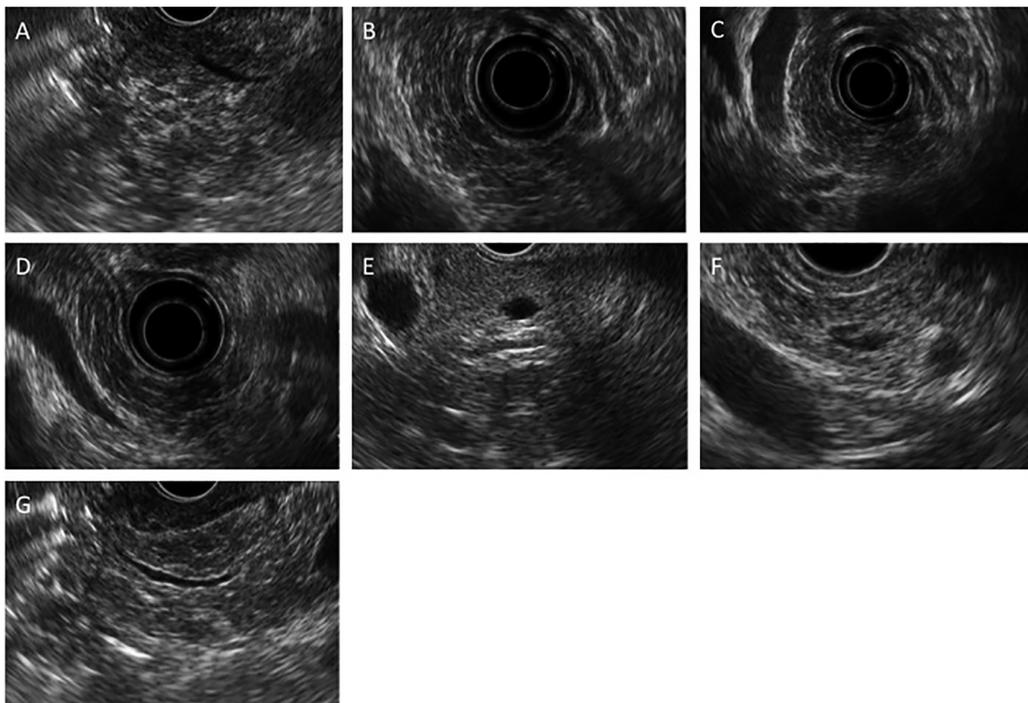


Fig. 1. EUS findings of early chronic pancreatitis

- A : Lobularity with honeycombing
- B : Lobularity without honeycombing
- C : Hyperechoic foci without shadowing
- D : Stranding
- E : Cyst
- F : Dilated side branches
- G : Hyperechoic MPD margin

#### Factors associated with the development of CP

##### *Drinking (Table 2, 3)*

Alcohol has been commonly reported as a risk

factor for CP. Alcohol consumption (80-150 g/day) is related to 60-80% of cases and patients usually have a long history of alcohol abuse (6-12 years)<sup>10-13)</sup>. Yadav *et al.*<sup>14)</sup> reported that compared with abstaining or light drinking, very heavy drinking was signifi-

Table 2. Main factors associated with the development of CP

Authors	Year		Odds ratio
<b>Drinking</b>			
Corrao <i>et al.</i> <sup>15)</sup>	2004	Drinkers of 25 g/day of alcohol vs. non-drinkers	1.34
Corrao <i>et al.</i> <sup>15)</sup>	2004	Drinkers of 50 g/day of alcohol vs. non-drinkers	1.78
Lin Y <i>et al.</i> <sup>13)</sup>	2001	Drinkers of 50-99 g/day of alcohol vs. non-drinkers	5.7
Corrao <i>et al.</i> <sup>15)</sup>	2004	Drinkers of 100 g/day of alcohol vs. non-drinkers	3.19
Lin Y <i>et al.</i> <sup>13)</sup>	2001	Drinkers of $\geq 100$ g/day of alcohol vs. non-drinkers	11.2
<b>Smoking</b>			
Nakamura T <i>et al.</i> <sup>22)</sup>	2012	Smokers vs. non-smokers	7.8

Table 3. Main factors associated with the risks for EUS pancreatic abnormalities

Authors	Year		Odds ratio
<b>Drinking</b>			
Yusoff <i>et al.</i> <sup>19)</sup>	2004	Heavy alcohol ingestion vs. non-drinkers	5.1
<b>Smoking</b>			
Yusoff <i>et al.</i> <sup>19)</sup>	2004	Heavy smoking vs. non-smokers	1.7

cantly associated with CP (odds ratio [OR], 3.10 ; 95% confidence interval [CI], 1.8-5.1). In addition, an epidemiological survey in Japan showed a significant dose-response relationship, where the higher the cumulative alcohol consumption (alcohol consumption per day  $\times$  years of drinking) is, the higher is the risk for CP ; this indicates that high long-term alcohol consumption increases the risk for CP. In fact, a case-control study conducted in Japan<sup>13)</sup> demonstrated that the OR of drinkers who had 50-99 g/day of alcohol and those who had  $\geq 100$  g/day compared to non-drinkers were 5.7 and 11.2, respectively ; this shows that the risk elevates in a dose-dependent manner. Corrao *et al.*<sup>15)</sup>, in a meta-analysis of drinking and 15 diseases including CP, stated that the relative risks for CP in drinkers of 25, 50, and 100 g/day compared to non-drinkers were 1.34, 1.78, and 3.19, respectively demonstrating a dose-dependent relationship : the risk for CP elevates as the alcohol assumption increases. On the other hand, there is a study reporting that less than 10% of heavy drinkers develop CP<sup>16)</sup>. Thus, it is also possible to interpret alcohol as only one of the factors for developing CP albeit a very important factor for finding CP in the early stages.

The relationship between drinking and EUS CP findings has also been reported. Thuler *et al.*<sup>17)</sup> compared alcoholic and non-alcoholic groups and demonstrated that alcoholic patients had significantly ( $P < 0.001$ ) more EUS abnormalities compared to non-alcoholic patients. Moreover, the two most

common features shared by alcoholic and non-alcoholic patients, according to the Catalano *et al.*<sup>18)</sup>, were heterogeneous echo-pattern and echogenic duct wall. Considering the Sahai *et al.*<sup>6)</sup>, the most common features for the alcoholic group were hyperechoic foci and hyperechoic duct while the non-alcoholic group showed more hyperechoic foci and hyperechoic strands. Yusoff *et al.*<sup>19)</sup> also demonstrated that heavy alcohol ingestion was associated with more EUS features of CP (OR 5.1 ; 95% CI, 3.1-8.5). Moreover, Sahai *et al.*<sup>20)</sup> reported that, in the analysis of alcohol consumption and EUS findings in 1,157 individuals, there were more EUS findings in CP as the alcohol consumption increased. Petrone *et al.*<sup>21)</sup> demonstrated that even at a low dose, alcohol consumption significantly increased the risk of hyperechoic parenchymal foci, main pancreatic duct (MPD) dilatation, and wall hyperechogenicity.

From these reports, asymptomatic, alcoholic patients might have pancreatic abnormalities that may be missed by other procedures, and EUS might be useful in screening patients for suspected early stage CP. We can also argue, based on these reports, that EUS is able to show early structural damage to the pancreas.

#### Smoking (Table 2, 3)

According to a case-control study in Japan, the risk for CP in smokers was higher (OR : 7.8) compared to non-smokers and smoking is shown to be

an independent factor from drinking<sup>22</sup>). Sankaran *et al.*<sup>23</sup> analyzed 14 studies, which included a total of 8,492 patients, and reported that alcohol use and smoking to be the largest risk factors for the development of CP with pooled prevalence values of 65% (95% CI, 48%–56%) and 61% (95% CI, 47%–73%), respectively. Yadav *et al.*<sup>14</sup> reported results from a multicenter study, and concluded that smoking was an important factor causing an increase incidence of CP. In that study, prior and current smoking were reported by 71.4% and 47.3% of CP patients, respectively. There are studies reporting that in patients who developed idiopathic CP at 35 years of age or older, calcification of pancreatic calculi occurred earlier and more frequently, accelerating the progression of CP in smokers compared to non-smokers<sup>24,25</sup>. Law *et al.*<sup>26</sup> also analyzed the relationship between CP and smoking and demonstrated a significant positive correlation between higher total smoking amounts and higher rates of being diagnosed with CP. They concluded that smoking is a distinct independent risk factor from drinking. Andriulli *et al.*<sup>27</sup> reported that since the relative risk for CP in smokers to non-smokers was 2.8, whereas that in former smokers was reduced to 1.4; smoking cessation significantly decreases the relative risk for CP. Yusoff *et al.*<sup>19</sup> also mentioned that one of the strongest independent predictors of severe EUS pancreatic abnormalities was heavy smoking (OR 1.7; 95% CI, 1.2–2.4). Petrone *et al.*<sup>21</sup> examined the relation of smoking and EUS findings and demonstrated that smoking was associated with an increased risk of hyperechoic parenchymal foci. Although smoking is frequently less recognized as a cause of CP compared to alcohol, it is an important risk factor.

#### *Past history of acute pancreatitis*

Various theories about the transition to CP after acute pancreatitis are proposed in the treatment guidelines for acute pancreatitis. However, at present, the necrosis-fibrosis theory<sup>28</sup>, that fibrosis after necrosis causes changes in the pancreatic duct which results in the progression to CP by causing the efflux disorder of pancreatic juice, is supported. In an analysis of the long-term outcomes in patients with acute pancreatitis in Japan<sup>29</sup>, the recurrence rate of all pancreatitis was 20.3% and the transition to CP was observed in 14.8% of patients. “Alcoholic” was the highest cause of the recurrence rate of pancreatitis (32.4%) as well as the transition rate to CP (26.0%). The transition rate to CP was 45% in patients who had recurrence twice, while it was

61.4% in those who had recurrence three times. Thus, the transition rate was high in patients who had multiple recurrences. Yasuda *et al.*<sup>30</sup> evaluated the outcome of severe acute pancreatitis and reported that transition to CP was noted in 22% of patients. In that study, the transition rate was higher in those with severe acute alcoholic pancreatitis than in those with severe acute biliary pancreatitis. In the report by Ammann *et al.*<sup>31</sup>, among 140 cases of alcoholic recurrent acute pancreatitis, 78% progressed to CP. Lankisch *et al.*<sup>32</sup> observed that 95% of the cases of CP had progressed from acute alcoholic pancreatitis. They also reported that the cumulative risk for the development of CP was 13% within 10 years and 16% within 20 years; the risk of CP in those who survived a second episode of acute pancreatitis was 38% within 2 years. Therefore, it is clear that the recurrent acute alcoholic pancreatitis progresses to CP. The understanding of this process is extremely important in the diagnosis and treatment of early CP. On the other hand, the investigations from the USA<sup>33</sup> showed a transition from acute to CP in 24.1% of patients after 3–5 years and 32.3% after 3–4 years, respectively. In this study, transition also occurred occasionally in patients with non-alcohol-induced pancreatitis. Nøjgaard *et al.*<sup>34</sup> reported that nicotine misuse increased the risk of progression from acute to CP substantially. Alcohol remains the most important factor for the transition from acute pancreatitis to CP, but cessation of smoking as well as drinking are needed to aid in preventing CP. On the other hand, Kumar *et al.*<sup>35</sup> examined the risk factors associated with pediatric CP. They clarified that the majority of children with CP (123 of 146 [84%]) reported prior recurrent episodes of acute pancreatitis. Based on the analysis in children, the transition from acute pancreatitis to CP may occur spontaneously or may be affected by factors other than drinking and smoking.

#### *Aging*

Ikedo *et al.*<sup>36</sup> analyzed the incidence of subclinical morphologic changes in the pancreas detected by screening ultrasonography in relation to the background factors of 130,951 subjects. In that study, an age-dependent increase in the incidence of MPD dilatation and cystic lesions was observed in both sexes whereas that of calcification was observed only in men. Petrone *et al.*<sup>21</sup> demonstrated that advanced age was significantly associated with an increased risk of MPD dilatation. In addition, Rajan *et al.*<sup>37</sup> analyzed the relationship between age and

the number of EUS findings in CP and observed that the number of EUS findings tended to increase with advancing age particularly in patients age 60 years and older.

Thus, it appears undeniable that aging is associated with the development of CP. However, changes in the pancreatic parenchyma and duct specifically due to aging should be taken into account as a factor in progression to CP. In fact, changes in the pancreas due to aging have been pathologically demonstrated. Detlefsen *et al.*<sup>38)</sup> screened pancreas specimens for the presence and pattern of fibrosis to determine the relationship between fibrosis, age, and duct lesions. In 89 postmortem specimens from individuals without any known pancreatic disease (age range 20–86 years), they found that fibrotic changes were significantly more common in individuals older than 60 years and the “normal” pancreas develops a specific type of focally accentuated fibrosis that is highly age related. In addition, Chantarojanasiri *et al.*<sup>39)</sup> examined the relation of aging and pancreatic changes in autopsy and imaging studies. They reported that the pancreatic volume was found to decrease with advancing age, and the pancreatic ductal structure was described as having a wide range of normal variations, although many other studies have shown a tendency toward enlargement with advancing age.

On EUS, the aging pancreas may exhibit abnormal findings similar to CP. Janssen *et al.*<sup>40)</sup> examined the effect of aging on pancreas elasticity by using semiquantitative EUS elastography; they reported that, on elastography, the pancreas become significantly harder during aging, but remain softer compared to that observed in CP. However, at present, it is difficult to definitively distinguish whether EUS findings in CP, considered to represent histological fibrosis, are age related. Thus, one should carefully diagnose CP in the elderly to avoid over-diagnosis.

#### Gallstone

Some reports showed an association between gallstones and CP. In a Chinese study, Wang *et al.*<sup>41)</sup> reported that the main etiologies of CP were alcohol (35.11%), biliary stones (34.36%), hereditary (7.22%), and idiopathic (12.90%); alcohol and biliary stones account for 70% of these causes. Another Chinese clinical study<sup>42)</sup> has also shown that the main cause of CP in China seems to be cholelithiasis, cholecystitis, or diseases of the choledochus. Hardt *et al.*<sup>43)</sup>, in an endoscopic retrograde cholangiopancreatography (ERCP) study, reported that 77% of

gallstone patients and only 47% of non-gallstone patients were found to have CP according to the Cambridge classification. According to the findings of Misra *et al.*<sup>44)</sup>, it seems that patients with gall stones tend to develop CP. In addition, Okazaki *et al.*<sup>45)</sup> performed a clinical study, in which they endoscopically measured pressures of the pancreatic duct and the sphincter of Oddi in patients with alcoholic pancreatitis, gallstone pancreatitis, and idiopathic CP, and controls. In that study, patients with alcoholic, gallstone-associated, and idiopathic CP had significantly higher pressures of the pancreatic duct and frequencies of the papillary sphincter waves compared to controls. Joergensen *et al.*<sup>46)</sup> reported a girl with gall stones associated with CP and an impacted gall stone in the ampulla of Vater. The passage of gallstones into the common bile duct may be involved in the etiology of gallstones pancreatitis. On the other hand, Yadav *et al.*<sup>47)</sup> reported that gallstones do not cause CP. Gallstones are the most common cause of acute pancreatitis. Amrann<sup>48)</sup> classified recurrent acute pancreatitis based on the clinical causes and reported that acute gallstone pancreatitis can become recurrent pancreatitis but it never progresses to CP. In a Japanese study<sup>29)</sup>, the transition from acute pancreatitis to CP was noted in 14.8%; it was high (26.0%) in alcoholic pancreatitis and low (1.7%) in gallstone pancreatitis. According to these past reports, the association of gallstones with CP remains controversial.

#### Gender

Durbecet *et al.*<sup>49)</sup> reported that before symptoms related to CP emerged, men consumed 1,161 L of alcohol over 18 years on average, while women only consumed 695 L over 11 years on average; this suggests that women are more susceptible to develop alcoholic pancreatitis. Possible factors causing such gender differences include the different drinking styles, genetics, and smaller liver and muscles in women facilitating an increase in blood alcohol levels. The gender differences may need to be taken into account when setting the amount of alcohol consumption at which drinking becomes a risk. Sankaran *et al.*<sup>23)</sup> reported that men were more likely compared to women to transition from acute pancreatitis to CP. There were some reports regarding the relations of gender and ultrasonographic findings. Ikeda *et al.*<sup>36)</sup> analyzed the subclinical morphologic changes in the pancreas on screening ultrasonography of 130,951 subjects in relation to their incidence and background factors. In that study, the incidence of MPD dilatation and calcification was

significantly higher in men ( $p < 0.0001$ ), whereas cystic lesions were significantly more frequent in women ( $p < 0.01$ ). Petrone *et al.*<sup>21</sup> also demonstrated that male gender was significantly associated with an increased risk of MPD dilatation.

### Conclusion

Although a method that definitively diagnoses early-stage CP has not been established, such a clinical stage is surely present during the progression of CP. Findings provided by the current literature review will add a considerable contribution to the understanding and diagnosing early stage CP.

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