

[ ORIGINAL ARTICLE ]

# Prevalence Rate and Predictive Factors of Pancreatic Diseases in Cases with Pancreatic Duct Dilatation: A Cross-sectional Study of a Large, Healthy Japanese Population

Toshio Fujisawa<sup>1,2</sup>, Hiroyuki Isayama<sup>1</sup>, Toshiaki Gunji<sup>3</sup>,  
Hajime Sato<sup>4</sup> and Nobuyuki Matsuhashi<sup>2</sup>

## Abstract:

**Objectives** To clarify the significance of ultrasonographically recorded pancreatic duct dilatation.

**Methods** Various parameters predicting pancreatic disease were evaluated in relation to pancreatic duct dilatation using data from medical checkups of healthy examinees.

**Results** Records of 281,384 subjects were analyzed. Pancreatic duct dilatation ( $\geq 3$  mm) was determined ultrasonographically in 524 patients (0.19%). Subsequent detailed examinations revealed the presence of pancreatic disease in 24.8% of these patients, including pancreatic cysts (15.6%) and chronic pancreatitis (4.9%). Pancreatic cancer was found in 6 cases (1.3%). Predictive factors of pancreatic diseases in examinees with pancreatic duct dilatation were investigated, and the diameter of the pancreatic duct ( $p < 0.001$ ) and HbA1c ( $p = 0.003$ ) were identified by a multivariate analysis. The diameter of the pancreatic duct ( $p < 0.013$ ), HbA1c ( $p = 0.009$ ), and body mass index ( $p = 0.032$ ) were identified as predictive factors in pancreatic cancer. The diameter of the pancreatic duct ( $p < 0.001$ ), age ( $p = 0.006$ ), and bilirubin ( $p = 0.020$ ) in pancreatic cyst as well as the diameter of the pancreatic duct ( $p < 0.001$ ), white blood cells ( $p = 0.022$ ), HbA1c ( $p = 0.033$ ), and alkaline phosphatase ( $p = 0.043$ ) in chronic pancreatitis were also identified. In patients with pancreatic duct dilatation, the optimal cut-off values were 3.5 mm and 6.1% for the pancreatic duct diameter and age, respectively, based on a receiver operating characteristic analysis.

**Conclusion** In cases with ultrasonography-determined pancreatic duct dilatation, subsequent detailed examinations of the pancreas were necessary because of the high-prevalence rate of 24.8%. In particular, marked pancreatic duct dilatation ( $\geq 3.5$  mm) and elevated HbA1c ( $\geq 6.1\%$ ) strongly suggest the presence of pancreatic diseases.

**Key words:** pancreatic duct dilatation, pancreatic cancer, intraductal papillary mucinous neoplasm, medical check, diameter of the pancreatic duct

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## Introduction

Pancreatic duct dilatation often suggests the presence of various pancreatic diseases, including chronic pancreatitis, pancreatic cancer, main duct or mixed type pancreatic intraductal papillary mucinous neoplasm (IPMN), and other pan-

creatic cystic/solid neoplasms involving the main pancreatic duct (1-3). Abdominal ultrasonography is a useful low-invasive tool for detecting pancreatic duct dilatation that is available for medical checkups of healthy subjects. In Japan, all company employees are required to undergo annual medical checkups. Therefore, a large subgroup of the population undergoes a comprehensive medical examination

<sup>1</sup>Department of Gastroenterology, Juntendo University School of Medicine, Japan, <sup>2</sup>Department of Gastroenterology, NTT Medical Center Tokyo, Japan, <sup>3</sup>Center for Preventive Medicine, NTT Medical Center Tokyo, Japan and <sup>4</sup>Department of Health Policy and Technology Assessment, National Institute of Public Health, Japan

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Correspondence to Dr. Hiroyuki Isayama, h-isayama@juntendo.ac.jp

every year, and abdominal ultrasonography is often included (4). Pancreatic duct dilatation is detected in a substantial proportion of this group. However, the epidemiology and clinical significance of pancreatic duct dilatation remain unclear.

Pancreatic cancer is an extremely aggressive, deadly disease, with little improvement in patient outcomes seen over the last two decades (5). Many cases are detected in unresectable conditions because of the difficulties associated with early detection (5-7). There is currently no good surveillance strategy for detecting resectable pancreatic cancer; however, abdominal ultrasonography is considered a promising surveillance procedure.

Pancreatic cysts are an extremely common entity identified on abdominal ultrasonography, and roughly 10% of individuals  $\geq 70$  years old have been diagnosed with this condition (8). It is believed that most of these cases are IPMN, although there are no definitive pathological data to support this hypothesis. Not only does IPMN have malignant potential itself, but it may also lead to the simultaneous development of pancreatic cancer in other parts of the pancreas (9). Therefore, the detection of pancreatic cysts may be a potential diagnostic clue for the early detection of pancreatic cancers. Furthermore, chronic pancreatitis is considered a risk factor for pancreatic cancer (10). The number of patients with chronic pancreatitis is increasing due to increasing alcohol consumption in Japan. Patients with chronic pancreatitis must therefore be closely monitored, as they constitute a high-risk group for pancreatic cancer.

In the present study, we investigated the incidence of pancreatic duct dilatation and the relationship between incidentally detected pancreatic duct dilatation and pancreatic diseases related to pancreatic cancer.

## Materials and Methods

### Study population

This retrospective study was conducted at two centers: the Center for Preventive Medicine, NTT Medical Center Tokyo, Tokyo, Japan; and the Center for Preventive Medicine, NTT Izu Medical Center, Shizuoka, Japan. Both institutes provide Early Disease Detection and Prevention programs for asymptomatic healthy adults. The majority of the study subjects were professionals of middle or high socioeconomic status working at offices around the Tokyo metropolitan area. Most (roughly 80%) of the participants were between 40 and 60 years old, as individuals in this age range are required to undergo an annual medical checkup.

All subjects participated in physical and physiological examinations, abdominal ultrasonography screening, blood test screening, and an interview with a physician. Clinical data were retrospectively retrieved from the institutional databases for analyses. All participants were informed that the clinical data obtained by the program might be retrospectively analyzed and published. All examinations included in

this study were performed as a routine part of the program, and none were aimed at collecting data specifically for the present study. Written informed consent was thus not required, and this study protocol was approved by the institutional ethics committees.

### Study design

Consecutive Japanese individuals who underwent comprehensive medical surveys, including abdominal ultrasonography, between January 1999 and April 2015 were enrolled in this study. Of these, subjects with pancreatic duct dilatation on ultrasonography screening were selected. The exclusion criteria were as follows: 1) a previous diagnosis of pancreatic duct dilatation, 2) a previous diagnosis of pancreatic disease, and 3) other pancreatic findings in addition to pancreatic duct dilatation on ultrasonography.

### Data collection

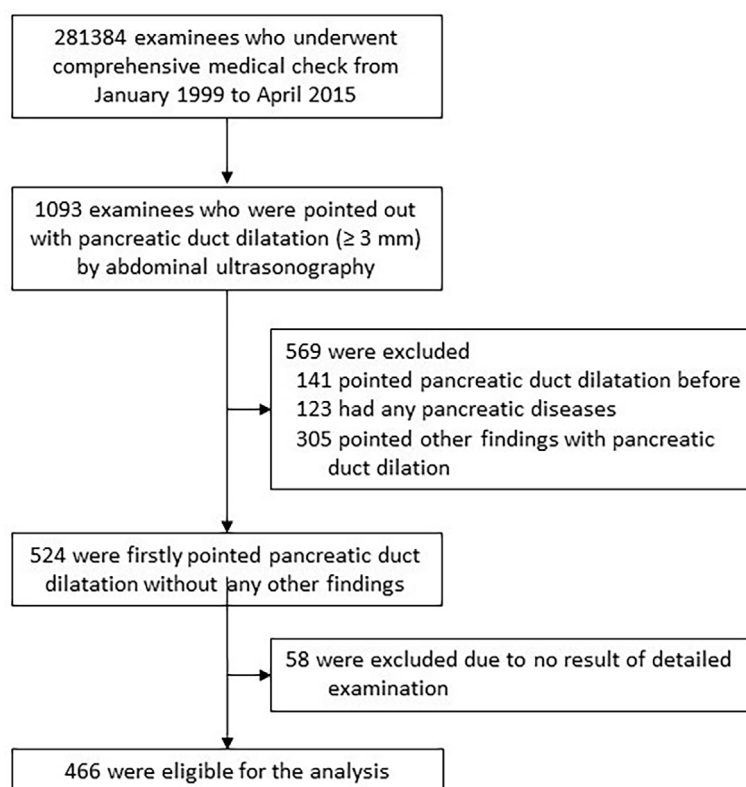
Anthropometric and metabolic data were collected in general physical examinations. The body mass index (BMI) was defined as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Serum and urine samples were collected from each participant after overnight fasting for 12 hours; the samples were immediately subjected to a biochemical analysis. Blood samples were tested using common enzymatic methods with an auto analyzer (Hitachi, Tokyo, Japan).

Abdominal ultrasonography was performed using a 3.5-MHz transducer. Pancreatic duct dilatation was diagnosed if the diameter of the main pancreatic duct in the pancreatic body was  $\geq 3$  mm, following the guidelines of abdominal screening ultrasonography published by the Japanese Society of Gastrointestinal Cancer Screening (11). These guidelines recommend that subjects diagnosed with pancreatic duct dilatation undergo an additional detailed examination of the pancreas.

A standardized questionnaire, which included items on the alcohol consumption and smoking status, was administered to all participants by the same trained team of interviewers. The validity of the information regarding alcohol consumption was confirmed in an interview with a physician. The total amount of alcohol consumed per week was calculated ( $\text{g}/\text{week}$ ). Lifetime smoking was described using the Brinkman index, which multiplies the years of smoking by the number of cigarettes consumed per day (12).

### Statistical analyses

Values are expressed as means or percentages. The association between pancreatic duct dilatation and each parameter was first investigated in a univariate analysis (continuous data and categorical parameters were analyzed using Student's *t*-test and Pearson's  $\chi^2$ -test, respectively), and then in a multivariate analysis. Factors with considerable influence on the prevalence of pancreatic disease in patients with pancreatic duct dilatation were determined using a multiple logistic regression analysis. The covariates used for the multi-



**Figure 1.** Flow chart of the subject selection. Among 281,384 individuals, 1,093 had pancreatic duct dilatation on abdominal ultrasonography and were included in this study. A total of 569 examinees were excluded according to the exclusion criteria. Finally, 524 subjects were included in the detailed analysis performed in this study.

variate analysis were gender, age, diameter of the pancreatic duct (mm), height (cm), weight (kg), BMI, abdominal circumference (cm), white blood cells, hemoglobin, platelets, total protein, albumin, uric acid, urea nitrogen, estimated glomerular filtration rate (GFR), sodium, potassium, chloride, calcium, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase ( $\gamma$ GTP), lactate dehydrogenase (LDH), amylase, glucose, glycosylated hemoglobin (HbA1c), thyroid stimulating hormone (TSH), C-reactive protein, history of *Helicobacter pylori* infection (based on *H. pylori* antibody positivity), history of hepatitis-B virus infection (based on HBs antigen or antibody positivity), history of hepatitis-C virus infection (based on HCV antibody positivity), alcohol consumption (g/week), and amount of smoking (Brinkman index). All urine sample parameters, including protein, glucose, urobilinogen, bilirubin, ketone bodies, and occult blood, were scored as qualitative parameters from 0-5 and analyzed using Student's *t*-test. Optimal cut-off values for the predictive factors were calculated using a receiver operating characteristic (ROC) analysis. All analyses were performed using the IBM SPSS Statistics 22 software program (IBM, Armonk, USA). A *p* value <0.05 was considered to indicate statistical significance (13).

## Results

### Pancreatic diseases in subjects with pancreatic duct dilatation

During the study period, a total of 281,384 subjects underwent comprehensive medical checkups, including abdominal ultrasonography. Among them, pancreatic duct dilatation ( $\geq 3$  mm) was newly found in 524 subjects (0.19%). A detailed examination of the pancreas is usually recommended in individuals with pancreatic duct dilatation. Fifty-eight (11.1%) of the 524 cases did not receive a detailed examination and were therefore excluded from the study. The remaining 466 cases were incorporated into the analysis. A flow chart of the subject selection is shown in Fig. 1.

A detailed examination revealed no disease (353 cases; 75.7%), pancreatic cysts (73 cases; 15.7%), chronic pancreatitis (23 cases; 4.9%), pancreatic cancer (6 cases; 1.3%), pancreas divisum (4 cases; 0.9%), and anomalous arrangement of the pancreaticobiliary ducts (4 cases; 0.9%), duodenal papillary neoplasm (2 cases; 0.4%), and IgG4-related pancreatitis (1 case; 0.2%) (Table 1). Thus, pancreatic diseases were found in a total of 113 cases (24.2%).

**Table 1. Result of Detailed Examination with Pancreatic Duct Dilatation.**

|   | Number | Percentage |
|---|--------|------------|
| No disease  | 353    | 75.7%      |
| Pancreatic cyst                                   | 73     | 15.7%      |
| Chronic pancreatitis                              | 23     | 4.9%       |
| Pancreatic cancer                                 | 6      | 1.3%       |
| Pancreas divisum                                  | 4      | 0.9%       |
| Anomalous arrangement of pancreaticobiliary ducts | 4      | 0.9%       |
| Duodenal papillary neoplasm                       | 2      | 0.4%       |
| IgG4 related pancreatitis                         | 1      | 0.2%       |
| Total   | 466    | 100%       |
| Withdrawn   | 58     | (11.1%)    |

### Predictive factors for pancreatic diseases related to pancreatic duct dilatation

We aimed to determine the factors that predict the presence of pancreatic disease in subjects with pancreatic duct dilatation. Various parameters, including the diameter of the pancreatic duct, were compared between subjects with and without pancreatic diseases (Table 2). Five factors, including the diameter of the pancreatic duct ( $p < 0.001$ ), glucose ( $p < 0.001$ ), HbA1c ( $p < 0.001$ ), urine glucose ( $p = 0.037$ ), and urine ketone body levels ( $p = 0.037$ ), were significantly higher in cases with pancreatic disease than in those without pancreatic disease. Before a multivariate analysis was performed, correlation coefficients among these factors were calculated (data not shown). Factors with a clinically apparent mutual association and absolute correlation coefficient value  $> 0.2$  were excluded from the analysis. HbA1c was taken to represent HbA1c and glucose and was included along with the urine glucose and urine ketone body levels in the multivariate analysis. A logistic regression analysis revealed that the diameter of the pancreatic duct ( $p < 0.001$ ) and HbA1c ( $p = 0.003$ ) were predictors of the presence of pancreatic disease in subjects with pancreatic duct dilatation (Fig. 2A).

### Predictive factors for pancreatic cancer

Only six cases of pancreatic cancer were newly detected because of pancreatic duct dilatation during the 16-year study period. Similar to the above analyses, various factors were compared between subjects with pancreatic cancer and without any diseases among examinees with pancreatic duct dilatation. A univariate analysis revealed that 9 factors, namely the diameter of the pancreatic duct ( $p = 0.002$ ), BMI ( $p = 0.010$ ), abdominal circumference ( $p = 0.032$ ), systolic blood pressure ( $p = 0.011$ ), diastolic blood pressure ( $p = 0.030$ ), white blood cell count ( $p = 0.036$ ), glucose ( $p < 0.001$ ), HbA1c ( $p < 0.001$ ), and urine glucose ( $p < 0.001$ ), were significantly associated with pancreatic cancer in subjects with pancreatic duct dilatation (Table 3). A logistic regression analysis revealed that 3 factors, namely the diameter of the pancreatic duct [odds ratio (OR) = 12.684,  $p = 0.013$ ], HbA1c

(OR=5.524,  $p = 0.009$ ), and BMI (OR=1.724,  $p = 0.032$ ), were predictive factors for pancreatic cancer (Fig. 2B).

### Predictive factors for pancreatic cysts and chronic pancreatitis

Pancreatic cysts and chronic pancreatitis are high-risk conditions for pancreatic cancer. Therefore, it is important to detect these diseases at an early stage. A univariate analysis revealed that 4 factors, namely the diameter of the pancreatic duct ( $p < 0.001$ ), age ( $p = 0.002$ ), estimated GFR ( $p = 0.009$ ), and bilirubin levels ( $p = 0.026$ ), in IPMN and 10 factors, namely the diameter of the pancreatic duct ( $p < 0.001$ ), white blood cell count ( $p = 0.001$ ), AST ( $p = 0.030$ ),  $\gamma$ GTP ( $p < 0.007$ ), glucose ( $p < 0.001$ ), HbA1c ( $p < 0.001$ ), urine protein ( $p = 0.007$ ), urine glucose ( $p = 0.001$ ), urine ketone bodies ( $p = 0.009$ ), and Brinkman index ( $p = 0.032$ ), in chronic pancreatitis were significantly different compared to subjects without pancreatic disease (Table 3). A logistic regression analysis revealed that 3 factors, namely the diameter of the pancreatic duct (OR=2.472,  $p < 0.001$ ), age (OR=1.040,  $p = 0.006$ ), and bilirubin (OR=2.769,  $p = 0.020$ ), were predictive of pancreatic cysts (Fig. 2C), and 4 factors, namely the diameter of the pancreatic duct (OR=3.860,  $p < 0.001$ ), white blood cell count (OR=1.332,  $p = 0.022$ ), HbA1c (OR=1.816,  $p = 0.033$ ), and AST (OR=1.022,  $p = 0.043$ ), were predictive of chronic pancreatitis (Fig. 2D).

### Pancreatic duct diameter as an indicator of pancreatic diseases

In all analyses, the diameter of the pancreatic duct was identified as a predictive factor in each disease. Therefore, the diameter of the pancreatic duct is the most important factor for detecting pancreatic disease. The mean diameter is summarized for each disease, and the percentages of the pancreatic diseases in each diameter range are described in Supplementary material 1. Similar to the logistic regression analysis results, the diameter of the pancreatic duct in pancreatic cancer, pancreatic cysts, and chronic pancreatitis was significantly larger than in cases without pancreatic diseases (Supplementary material 2).

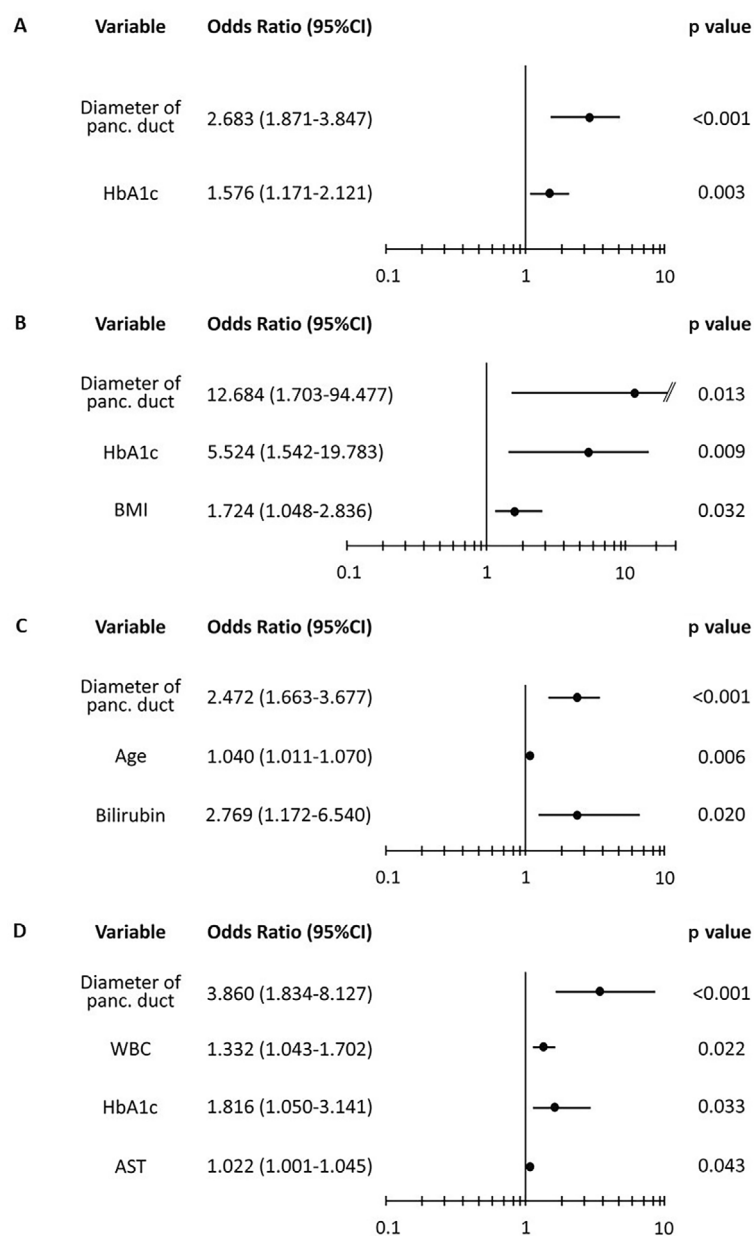
**Table 2. Comparison between Examinees with and without Any Pancreatic Diseases.**

|                                    | With disease<br>(n=113) | Without disease<br>(n=353) | P      |
|------------------------------------|-------------------------|----------------------------|--------|
| Female                             | 12.0%                   | 10.2%                      | 0.512  |
| Age                                | 58.6±9.3                | 56.6±9.4                   | 0.051  |
| Diameter of pancreatic duct (mm)   | 4.12±1.59               | 3.38±0.53                  | <0.001 |
| Height (cm)                        | 166.8±7.3               | 167.8±7.4                  | 0.183  |
| Weight (kg)                        | 63.4±10.6               | 65.2±9.0                   | 0.068  |
| BMI (kg/m <sup>2</sup> )           | 22.7±3.2                | 23.1±2.5                   | 0.179  |
| Abdominal circumference (cm)       | 83.0±9.0                | 84.6±7.5                   | 0.127  |
| Systolic blood pressure (mmHg)     | 128.1±17.6              | 127.7±18.0                 | 0.826  |
| Diastolic blood pressure (mmHg)    | 79.1±10.2               | 79.7±11.0                  | 0.606  |
| White blood cell (×1,000 cells/μL) | 5.66±1.7                | 5.67±1.7                   | 0.954  |
| Hemoglobin (g/dL)                  | 14.4±1.4                | 14.6±1.2                   | 0.140  |
| Platelet (×10,000 cells/μL)        | 22.3±4.6                | 22.5±5.7                   | 0.843  |
| Total protein (g/dL)               | 7.17±0.39               | 7.10±0.41                  | 0.111  |
| Albumin (g/dL)                     | 4.41±0.29               | 4.42±0.29                  | 0.663  |
| Uric acid (mg/dL)                  | 5.97±1.32               | 5.91±1.22                  | 0.681  |
| Urea nitrogen (mg/dL)              | 14.7±5.1                | 14.3±4.4                   | 0.409  |
| Estimated GFR (mL/min)             | 71.5±17.2               | 73.8±15.1                  | 0.170  |
| Sodium (mEq/L)                     | 141±2.4                 | 141±1.9                    | 0.215  |
| Potassium (mEq/L)                  | 4.38±0.39               | 4.37±0.35                  | 0.854  |
| Chloride (mEq/L)                   | 104±3.4                 | 104±2.3                    | 0.219  |
| Calcium (mEq/L)                    | 9.25±0.32               | 9.29±0.33                  | 0.411  |
| Triglyceride (mg/dL)               | 113±84.1                | 113±70.8                   | 0.940  |
| HDL (mg/dL)                        | 61.6±17.9               | 60.5±15.5                  | 0.518  |
| LDL (mg/dL)                        | 115±30.0                | 115±30.7                   | 0.762  |
| Total bilirubin (mg/dL)            | 0.83±0.29               | 0.82±0.29                  | 0.854  |
| AST (U/L)                          | 26.3±18.0               | 24.9±10.9                  | 0.333  |
| ALT (U/L)                          | 23.0±12.4               | 23.6±12.5                  | 0.610  |
| ALP (U/L)                          | 200±53.4                | 205±58.5                   | 0.478  |
| γGTP (IU/L)                        | 55.3±67.5               | 50.0±48.7                  | 0.360  |
| LDH (IU/L)                         | 185±43.6                | 195±57.4                   | 0.097  |
| Amylase (IU/L)                     | 82.1±36.5               | 80.5±30.9                  | 0.656  |
| Glucose (mg/dL)                    | 112±39.0                | 102±18.4                   | <0.001 |
| HbA1c (%)                          | 6.03±1.21               | 5.69±0.57                  | <0.001 |
| TSH (μU/mL)                        | 1.84±1.36               | 1.70±1.41                  | 0.397  |
| C-reactive protein (mg/dL)         | 0.11±0.42               | 0.07±0.14                  | 0.344  |
| Urine protein*                     | 0.26±0.73               | 0.17±0.50                  | 0.131  |
| Urine glucose*                     | 0.20±0.89               | 0.06±0.43                  | 0.037  |
| Urine urobilinogen*                | 1.00±0.00               | 1.00±0.00                  | 1.000  |
| Urine bilirubin*                   | 0.00±0.00               | 0.00±0.00                  | 1.000  |
| Urine ketone body*                 | 0.13±0.44               | 0.05±0.25                  | 0.037  |
| Urine occult blood*                | 0.21±0.68               | 0.24±0.72                  | 0.651  |
| History of HBV infection           | 13.3%                   | 12.9%                      | 0.650  |
| History of HCV infection           | 2.9%                    | 1.3%                       | 0.277  |
| Alcohol consumption (g/week)       | 3.38±2.78               | 3.93±2.58                  | 0.064  |
| Brinkman index                     | 396±403                 | 340±381                    | 0.361  |

Data are shown as mean±standard deviation or percentage.

\*Factors in urine were evaluated as categorical numbers from 0 to 5.

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GFR: glomerular filtration rate, HBV: hepatitis-B virus, HCV: hepatitis-C virus, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein, IPMN: intraductal papillary mucinous neoplasm, LDH: lactate dehydrogenase, LDL: low-density lipoprotein, TSH: thyroid stimulating hormone, γGTP: gamma-glutamyl transpeptidase, ROC: receiver operating characteristic



**Figure 2.** Results of the logistic regression analysis. **A:** Predictive factors for the presence of any pancreatic disease in patients with pancreatic duct dilatation. **B:** Predictive factors for pancreatic cancer. **C:** Predictive factors for pancreatic cysts. **D:** Predictive factors for chronic pancreatitis.

### Optimal cut-off value of the predictors of pancreatic diseases

An ROC analysis was performed to detect the optimal cut-off value of two of the predictive factors (diameter of pancreatic duct and HbA1c) for any pancreatic diseases in subjects with pancreatic duct dilatation (Fig. 3). The areas under the ROC curve were 0.666 and 0.578, and the optimal cut-off levels were 3.5 mm and 6.1% for pancreatic duct diameter and HbA1c, respectively.

## Discussion

### Prevalence

The rate of pancreatic duct dilatation ( $\geq 3$  mm) in all study participants was 0.19%, which was less than anticipated, as Tanaka et al. previously reported a rate of 1.21% (9). However, the subjects included in the present study were different from those in that study, as our population was composed of healthy subjects, while that of Tanaka et al. had health problems, which may have caused this discrepancy.

Pancreatic duct dilatation does not necessarily indicate the presence of pancreatic disease, as some are simply cases of physiogenic pancreatic duct dilatation (14). In the present

**Table 3. Comparison among Examinees with Each Disease and without Disease.**

|                                    | Pancreatic cancer<br>(n=6) | Pancreatic cyst<br>(n=73) | Chronic pancreatitis<br>(n=23) | No disease<br>(n=353) |
|------------------------------------|----------------------------|---------------------------|--------------------------------|-----------------------|
| Female                             | 0%                         | 16.2%                     | 4.3%                           | 10.2%                 |
| Age                                | 59.3±4.8                   | 60.4±9.4†                 | 53.9±8.4                       | 56.6±9.4              |
| Diameter of pancreatic duct (mm)   | 4.08±1.14†                 | 3.86±1.11‡                | 5.20±2.61‡                     | 3.38±0.53             |
| Height (cm)                        | 166.8±5.1                  | 166.9±7.2                 | 167.0±8.8                      | 167.9±7.5             |
| Weight (kg)                        | 71.8±7.9                   | 63.7±10.1                 | 62.8±12.8                      | 65.3±9.0              |
| BMI (kg/m <sup>2</sup> )           | 25.9±3.6†                  | 22.8±3.0                  | 22.4±3.5                       | 23.1±2.5              |
| Abdominal circumference (cm)       | 94.0±11.1*                 | 84.2±8.4                  | 80.5±9.8                       | 84.6±7.5              |
| Systolic blood pressure (mmHg)     | 146.5±13.9*                | 128.2±16.3                | 128.3±19.8                     | 127.7±18.0            |
| Diastolic blood pressure (mmHg)    | 89.5±8.0*                  | 78.9±9.4                  | 79.1±12.3                      | 79.7±11.0             |
| White blood cell (×1,000 cells/μL) | 7.12±1.72*                 | 5.26±1.4                  | 6.87±1.87†                     | 5.67±1.67             |
| Hemoglobin (g/dL)                  | 15.2±1.9                   | 14.5±1.3                  | 14.3±1.7                       | 14.6±1.2              |
| Platelet (×10,000 cells/μL)        | 20.5±4.7                   | 21.7±3.6                  | 24.7±6.3                       | 22.5±5.7              |
| Total protein (g/dL)               | 7.32±0.53                  | 7.16±0.37                 | 7.26±0.46                      | 7.10±0.41             |
| Albumin (g/dL)                     | 4.43±0.24                  | 4.42±0.26                 | 4.40±0.37                      | 4.42±0.29             |
| Uric acid (mg/dL)                  | 5.73±0.95                  | 5.97±1.3                  | 6.19±1.63                      | 5.91±1.22             |
| Urea nitrogen (mg/dL)              | 11.4±2.8                   | 15.4±5.8                  | 13.7±3.7                       | 14.3±4.4              |
| Estimated GFR (mL/min)             | 74.4±5.8                   | 68.7±16.2†                | 76.5±20.8                      | 73.8±15.1             |
| Sodium (mEq/L)                     | 140±1.5                    | 141±2.0                   | 141±3.8                        | 142±1.9               |
| Potassium (mEq/L)                  | 4.37±0.06                  | 4.36±0.37                 | 4.41±0.55                      | 4.38±0.35             |
| Chloride (mEq/L)                   | 104±2.3                    | 104±2.8                   | 104±6.0                        | 105±2.3               |
| Calcium (mEq/L)                    | 9.07±0.49                  | 9.29±0.31                 | 9.26±0.32                      | 9.29±0.33             |
| Triglyceride (mg/dL)               | 112±36.9                   | 114±91.8                  | 118±75.0                       | 113±70.9              |
| HDL (mg/dL)                        | 51.5±7.3                   | 62.4±18.4                 | 61.4±20.2                      | 60.5±15.5             |
| LDL (mg/dL)                        | 128±35.0                   | 116±26.9                  | 110±35.3                       | 116±30.7              |
| Total bilirubin (mg/dL)            | 0.62±0.12                  | 0.90±0.30*                | 0.73±0.24                      | 0.82±0.29             |
| AST (U/L)                          | 24.2±9.5                   | 25.4±14.9                 | 30.8±29.0*                     | 24.9±10.9             |
| ALT (U/L)                          | 24.8±18.6                  | 22.0±11.2                 | 25.6±15.4                      | 23.6±12.5             |
| ALP (U/L)                          | 217±40.4                   | 194±53.0                  | 222±48.3                       | 205±58.5              |
| γGTP (IU/L)                        | 34.3±21.1                  | 50.0±57.1                 | 81.5±103.4†                    | 50.0±48.7             |
| LDH (IU/L)                         | 218±82.4                   | 186±42.5                  | 181±37.6                       | 195±57.4              |
| Amylase (IU/L)                     | 67.2±29.2                  | 81.3±30.2                 | 86.9±55.4                      | 80.5±31.0             |
| Glucose (mg/dL)                    | 143±80.8‡                  | 106±26.4                  | 125±57.1‡                      | 102±18.4              |
| HbA1c (%)                          | 6.98±2.04‡                 | 5.85±0.95                 | 6.40±1.66‡                     | 5.69±0.58             |
| TSH (μU/mL)                        | 1.65±1.08                  | 1.90±1.39                 | 1.41±0.92                      | 1.70±1.41             |
| C-reactive protein (mg/dL)         | 0.31±0.26                  | 0.12±0.51                 | 0.08±0.09                      | 0.07±0.14             |
| Urine protein*                     | 0.00±0.00                  | 0.22±0.63                 | 0.50±1.06†                     | 0.17±0.50             |
| Urine sugar*                       | 1.00±2.24‡                 | 0.08±0.37                 | 0.45±1.47†                     | 0.06±0.43             |
| Urine urobilinogen*                | 1.00±0.00                  | 1.00±0.00                 | 1.00±0.00                      | 1.00±0.00             |
| Urine bilirubin*                   | 0.00±0.00                  | 0.00±0.00                 | 0.00±0.00                      | 0.00±0.00             |
| Urine ketone body*                 | 0.20±0.45                  | 0.11±0.36                 | 0.23±0.69†                     | 0.05±0.25             |
| Urine occult blood*                | 0.00±0.00                  | 0.17±0.55                 | 0.27±0.77                      | 0.24±0.72             |
| History of HBV infection           | 16.70%                     | 13.7%                     | 8.7%                           | 12.9%                 |
| History of HCV infection           | 0%                         | 4.1%                      | 0%                             | 1.3%                  |
| Alcohol consumption (g/week)       | 4.00±3.00                  | 3.65±2.68                 | 3.00±2.94                      | 3.93±2.58             |
| Brinkman index                     | 472±472                    | 376±436                   | 534±307*                       | 359±381               |

Data are shown as mean±standard deviation or percentage.

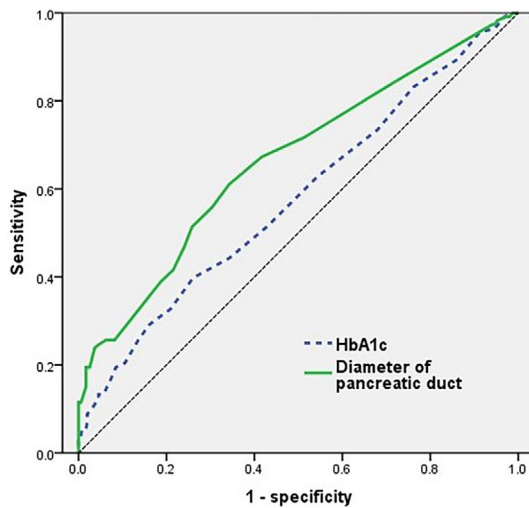
p values in each disease were calculated to no disease, \*p<0.05, †p<0.01, ‡p<0.001.

study, a subsequent detailed examination revealed pancreatic disease in 24.2% of patients with pancreatic duct dilatation. Generally, the prevalence rate of pancreatic disease among middle-aged individuals (40-60 years old) is reported to be <10%, although reliable data do not exist. Therefore, individuals with pancreatic duct dilation are a high-risk group for pancreatic disease, and they should receive follow-up ex-

aminations.

### Predictive factors

The predictive factors for each pancreatic disease were investigated. The diameter of the pancreatic duct was the only common predictive factor among the three most important pancreatic diseases. However, a multivariate analysis re-



**Figure 3.** Results of the receiver operating characteristic (ROC) curve analysis of the predictors of pancreatic diseases in patients with pancreatic duct dilatation. The areas under the curve (AUC) were 0.666 and 0.578 for pancreatic duct diameter and HbA1c, respectively. The diagonal line shows the reference.

vealed that the HbA1c and BMI were additional predictive factors for pancreatic cancer; the age and bilirubin level were additional predictive factors for pancreatic cysts; and the HbA1c, white blood cell count and AST level were additional predictive factors for chronic pancreatitis. Of those factors, only HbA1c was a common predictive factor between pancreatic cancer and chronic pancreatitis; the other factors were unique to each disease. These factors are reasonably associated with the respective diseases based on pathophysiology. Indeed, diabetes mellitus and obesity are well-known risk factors for pancreatic cancer. IPMN is prevalent among elderly people, and obstructive jaundice is among the high-risk stigmata of IPMN (15). Chronic pancreatitis causes impaired glucose tolerance and increases the white blood cell count in the peripheral blood by inducing inflammation. In addition, elevation of the AST level may reflect alcoholic liver damage.

### Alcohol consumption in chronic pancreatitis

However, alcohol consumption was not included in the list of predictive factors for chronic pancreatitis. It is natural to consider alcohol consumption as the most important predictive factor for chronic pancreatitis because it is the strongest catalyst of this condition (16). This contradiction seems to have been a result of the limitations of the present study. Data concerning alcohol consumption gathered in this study were based on the amount of alcohol consumed during the period in which the health checkup was performed; therefore, the drinking history was not accurately represented. Indeed, 7 of 23 patients with chronic pancreatitis were classified as non-drinkers because they underwent their health checkup during a period of abstinence. Furthermore, the data were self-reported. Heavy drinkers tend to underre-

port the amount of alcohol they consume due to a sense of guilt (17). In fact, the levels of  $\gamma$ GTP, which reflects alcohol consumption, were significantly higher in the chronic pancreatitis group than in the no disease group ( $81.5 \pm 103.4$  vs.  $50.0 \pm 48.7$  IU/L,  $p=0.007$ ) in the univariate analysis. These factors might have affected the results of the present analysis of the relationship between alcohol consumption and chronic pancreatitis. An index capable of evaluating past alcohol consumption may be useful in such an analysis.

### Optimal cut-off values for detecting pancreatic diseases

The ROC curve analysis revealed the optimal cut-off values for the diameter of the pancreatic duct (3.5 mm) and HbA1c (6.1%) for detecting pancreatic diseases in individuals with pancreatic duct dilatation. Therefore, individuals with pancreatic duct dilatation  $>3.5$  mm and HbA1c  $>6.1\%$  should undergo a careful and thorough examination of the pancreas. If such individuals also present with obesity (i.e., a high BMI), pancreatic cancer must be ruled out. The presence of jaundice can assist in detecting pancreatic cysts, and elevations in the white blood cell count and AST level can be helpful for detecting chronic pancreatitis.

### Limitations

This study was not without limitations. First, the data were retrospectively analyzed, but the status of the examinees and the transducer type changed over the study period. Second, the number of participants ( $n=58$ , 11.0%) who did not receive a detailed examination and were classified as having withdrawn was high. Third, it is sometimes difficult to visualize the entire pancreas during abdominal ultrasonography due to intestinal gas and the presence of a thick fat pad. However, the data of the present study did not capture the degree to which the pancreas was observed.

The present study revealed the incidence and significance of pancreatic duct dilatation in healthy subjects. Several factors, including the pancreatic duct diameter and HbA1c, were revealed as predictive factors for pancreatic disease. Although the prevalence of any pancreatic disease in patients with pancreatic duct dilatation is not high, these factors will be useful for the early detection of pancreatic diseases.

**The authors state that they have no Conflict of Interest (COI).**

### References

1. Tanaka S, Nakao M, Ioka T, et al. Slight dilatation of the main pancreatic duct and presence of pancreatic cysts as predictive signs of pancreatic cancer: a prospective study. *Radiology* **254**: 965-972, 2010.
2. Nakajima Y, Yamada T, Sho M. Malignant potential of intraductal papillary mucinous neoplasms of the pancreas. *Surg Today* **40**: 816-824, 2010.
3. Maisonneuve P, Lowenfels AB. Chronic pancreatitis and pancreatic cancer. *Dig Dis* **20**: 32-37, 2002.



4. Gunji T, Matsuhashi N, Sato H, et al. *Helicobacter pylori* infection is significantly associated with metabolic syndrome in the Japanese population. *Am J Gastroenterol* **103**: 3005-3010, 2008.
5. Zhang Q, Zeng L, Chen Y, et al. Pancreatic cancer epidemiology, detection, and management. *Gastroenterol Res Pract* **2016**: 8962321, 2016.
6. Cartwright T, Richards DA, Boehm KA. Cancer of the pancreas: are we making progress? A review of studies in the US Oncology Research Network. *Cancer Control* **15**: 308-313, 2008.
7. Fujisawa T, Joshi B, Nakajima A, Puri RK. A novel role of interleukin-13 receptor alpha2 in pancreatic cancer invasion and metastasis. *Cancer Res* **69**: 8678-8685, 2009.
8. Stark A, Donahue TR, Reber HA, Hines OJ. Pancreatic cyst disease: a review. *JAMA* **315**: 1882-1893, 2016.
9. Tanaka S, Nakaizumi A, Ioka T, et al. Main pancreatic duct dilatation: a sign of high risk for pancreatic cancer. *Jpn J Clin Oncol* **32**: 407-411, 2002.
10. DiMagno EP, DiMagno MJ. Chronic pancreatitis: landmark papers, management decisions, and future. *Pancreas* **45**: 641-650, 2016.
11. Mizuma Y, Fukushima T, Kukita K. Critical Assessment of Follow-up Guideline on Abdominal Ultrasound Screening: Comparative Examination of "Categorized Criteria for Abdominal Ultrasound Cancer Screening" and "Abdominal Ultrasound Results Classification and Follow-up Guideline" by the Japan Society of Ningen Dock. *Nihon Shokaki Gan Kenshin Gakkai zasshi* **51**: 234-242, 2013 (in Japanese, Abstract in English).
12. Gunji T, Sato H, Iijima K, et al. Risk factors for erosive esophagitis: a cross-sectional study of a large number of Japanese males. *J Gastroenterol* **46**: 448-455, 2011.
13. Fujisawa T, Kagawa K, Hisatomi K, et al. Obesity with abundant subcutaneous adipose tissue increases the risk of post-ERCP pancreatitis. *J Gastroenterol* **51**: 931-938, 2016.
14. Bolondi L, Gaiani S, Gullo L, Labo G. Secretin administration induces a dilatation of main pancreatic duct. *Dig Dis Sci* **29**: 802-808, 1984.
15. Kim YI, Shin SH, Song KB, et al. Branch duct intraductal papillary mucinous neoplasm of the pancreas: single-center experience with 324 patients who underwent surgical resection. *Korean J Hepatobiliary Pancreat Surg* **19**: 113-120, 2015.
16. Majumder S, Chari ST. Chronic pancreatitis. *Lancet* **387**: 1957-1966, 2016.
17. Gunji T, Matsuhashi N, Sato H, et al. Light and moderate alcohol consumption significantly reduces the prevalence of fatty liver in the Japanese male population. *Am J Gastroenterol* **104**: 2189-2195, 2009.

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