

## Analysis of Comorbidity for Patients with Pancreatic Cysts in Medical Checkup Screening

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**Objectives:** We investigated whether there is a difference in the frequency of comorbidity between patients with pancreatic cysts and those without pancreatic cysts by abdominal ultrasonography in patients undergoing medical checkup screening.

**Methods:** The subjects were 6,627 patients who underwent abdominal ultrasonography at Tokai University Hachioji Hospital's Health Screening Center between April 2019 and March 2020.

**Results:** Of the total 6,627 patients, 158 (2.4%) were pointed out to have pancreatic cysts. Multivariate analysis revealed that the related factors were female sex, age 60 years or older, diabetes, lung cancer, and uterine/ovarian cancer.

**Conclusion:** Unlike pancreatic cancer, pancreatic cysts are more common in women. In addition, it is known that pancreatic cysts have a high complication rate of cancers of other organs; lung cancer and uterine/ovarian cancer were identified as high-risk factors in this study.

**Key words:** pancreatic cysts, ultrasonography, medical checkup screening, pancreatic cancer

### INTRODUCTION

Pancreatic cancer has the poorest prognosis among all cancer types; the 5-year survival rate for pancreatic cancer is 7.9% for men and 7.5% for women, which is significantly lower than the common 5-year survival rate for all cancer types (62.0% for men and 66.9% for women) [1]. The high-risk factors for pancreatic cancer include old age, family history, diabetes, obesity as well as a history of chronic pancreatitis, pancreatic cysts, smoking, and drinking. Most pancreatic cysts are found accidentally on abdominal ultrasonography, including screening and medical checkup screening [2-5]. Appropriate additional scrutiny of patients with pancreatic cysts identified using abdominal ultrasonography and regular follow-up enables early detection of pancreatic cancer and reduction of mortality, and many screening methods are being attempted [6].

There are few reports on high-risk factors for pancreatic cysts, and it is thought that identifying high-risk factors for pancreatic cysts and performing efficient screening will lead to early detection of pancreatic cancer and contribute to improving the prognosis.

Regarding screening for pancreatic cysts, detailed systemic screening and interviews for the underlying medical history are restricted in ordinary medical care because of the burden on each case. During a medical checkup screening, the whole body is screened and the

detailed medical history can be heard in the interview; therefore, we thought that the detailed information obtained in the medical checkup screening would be useful for clarifying the natural history and risk factors of pancreatic cysts.

In this study, we compared the clinical factors of cases in which pancreatic cysts were identified in our hospital's medical checkup screening with the clinical factors of the remaining population, and examined whether there was a difference in the frequency of comorbidity.

### PATIENTS AND METHODS

The subjects in the study were 6627 patients (4050 men and 2577 women) who underwent abdominal ultrasonography at Tokai University Hachioji Hospital's health screening center from April 1, 2019, to March 31, 2020. The items to be examined were sex, age, abdominal ultrasonography findings, life history, and primary medical history based on the retrospective questionnaire written by the examinee.

Abdominal ultrasonography was performed by a specialized sonographer based on the scanning method recommended by the Japanese Society of Gastrointestinal Cancer Screening. A pancreatic cyst diameter of 5 mm or more is required for close examination in accordance with the judgment manual of the Society [7].

**Table 1** Frequency of comorbidity disorder in our health examinations

Groups	Pancreatic Cyst	Without PC	All Examinees
Drinking history	84 (53.2%)	4164 (64.4%)	4248 (63.7%)
Smoking history	15 (9.5%)	1045 (16.2%)	1060 (15.9%)
Lifestyle-related diseases			
Hypertension	55 (34.8%)	1507 (23.3%)	1562 (23.4%)
Diabetes	25 (15.8%)	448 (6.9%)	473 (7.1%)
Dyslipidemia	52 (32.9%)	1384 (21.4%)	1436 (21.5%)
Hyperuricemia	10 (6.3%)	588 (9.1%)	598 (9.0%)
Gastrointestinal diseases			
Gastric polyp	20 (12.7%)	655 (10.1%)	675 (10.1%)
Colon polyp	24 (15.2%)	680 (10.5%)	704 (10.6%)
Gallbladder polyp	43 (27.2%)	218 (3.4%)	261 (3.9%)
Gallbladder stone	8 (5.1%)	223 (3.4%)	231 (3.5%)
Pancreatitis	1 (0.6%)	22 (0.3%)	23 (0.3%)

**Table 2** History/primary medical history of malignant disease in our health examinations

Groups	Pancreatic Cyst	Without PC	All Examinees
Gastric cancer	5 (3.2%)	50 (0.8%)	55 (0.8%)
Colon cancer	3 (1.9%)	70 (1.1%)	73 (1.1%)
Liver cancer	0	4 (0.06%)	4 (0.06%)
Biliary tract cancer	0	3 (0.04%)	3 (0.04%)
Lung cancer	3 (1.9%)	17 (0.3%)	20 (0.3%)
Prostate cancer	0	78 (2.0%)	78 (2.0%)
Breast cancer	2 (2.0%)	94 (3.8%)	96 (3.7%)
Uterine/Ovarian cancer	3 (3.0%)	37 (1.5%)	40 (1.6%)

Of the life history, the drinking and smoking history were based on the individual's declaration. A habit of daily or few times a week alcohol consumption and the consumption of  $\geq 21.6$  g alcohol per day were deemed to constitute a drinking history. If the individual had smoked 100 or more cigarettes within the past 6 months, and 1 or more cigarettes were smoked daily within the last 1 month, they were deemed to have a smoking history.

The history of primary diseases is divided into (1) lifestyle-related diseases, (2) gastrointestinal diseases, and (3) cancers. Lifestyle-related diseases and cancer were selected as typical diseases with large number of morbidities, and gastrointestinal diseases were selected as acquired benign diseases that are frequently identified using ultrasonography or endoscopy. The lifestyle-related diseases included were: (1) hypertension, (2) diabetes, (3) dyslipidemia, and (4) hyperuricemia. The gastrointestinal diseases included were: (1) gastric polyps, (2) colon polyps, (3) gallbladder polyps, (4) cholelithiasis, and (5) pancreatitis. The cancers included were (1) gastric cancer, (2) colon cancer, (3) liver cancer, (4) biliary tract cancer, (5) lung cancer, (6) prostate cancer, (7) breast cancer, and (8) uterine/ovarian cancer. Regarding the determination of each disease, those who have been treated for the disease at our hospital and disease name registration can be confirmed in the medical record are considered to have a disease. Those who have not been treated for the disease at our hospital are treated based on individual declarations.

The t-test was used as a statistical method to compare the mean values between the two groups, and Pearson's chi-square test was used to compare the proportions between the two groups. Multivariate analysis

was performed using the nominal logistic regression analysis for factors related to the frequency of pancreatic cysts. Statistical analysis was performed using JMP14 (JMP International Offices, Tokyo, Japan). A p value less than 0.05 was deemed statistically significant.

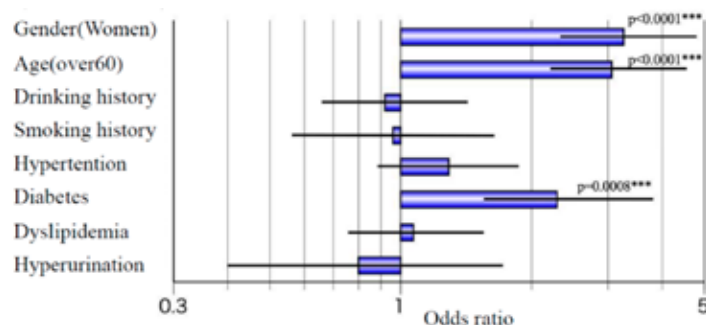
All subjects provided written informed consent for the use of their health records for analysis. This study was approved by the Ethics Committee of Tokai University (No. 20R-018) and was conducted in accordance with the Declaration of Helsinki.

## RESULTS

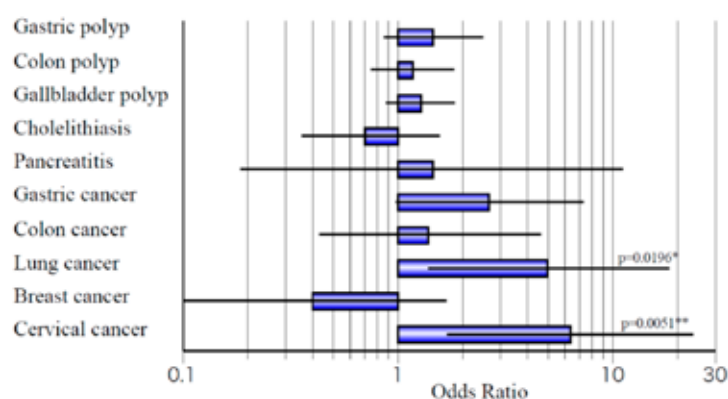
Of the 6627 examinees, 158 (2.4%) were pointed out to have pancreatic cysts. The total number of examinees was 4050 men (61.1%) and 2577 women (38.9%); there were 59 men (46.8%) and 99 women (53.2%) in the pancreatic cyst group. The mean age of all examinees was  $54.1 \pm 11.0$  years (median 53 years), while that of the pancreatic cyst indication group was  $63.0 \pm 11.1$  years, and the pancreatic cyst group was 9 years older.

Life history, lifestyle-related diseases, and digestive system diseases are shown in Table 1. The drinking history was 4248 (63.7%) in all examinees, compared to 84 (53.2%) in the pancreatic cyst group. The smoking history was 1060 (15.9%) in all examinees, compared to 15 (9.5%) in the pancreatic cyst group. Regarding lifestyle-related diseases, hypertension was present in 1562 (23.4%), diabetes was present in 473 (7.1%), dyslipidemia was present in 1436 (21.5%), and hyperuricemia was present in 598 (9.0%) participants. In the pancreatic cyst group, hypertension was present in 55 (34.8%), diabetes was present in 25 (15.8%), dyslipidemia was present in 52 (32.9%), and hyperuri-

**Table 3** Examination of factors related to comorbidity of pancreatic cyst (nominal logistic regression analysis)



**Table 4** Examination of factors related to comorbidity of pancreatic cyst (nominal logistic regression analysis)



**Table 5** Examination of factors related to comorbidity of pancreatic cyst (nominal logistic regression analysis)

	Odds Ratio	95% Confidence interval	p value
Gender (Women)	3.26	2.21-4.79	< 0.0001
Age (over 60)	3.06	2.12-4.41	< 0.0001
Diabetes	2.29	1.41-3.72	0.0008
Lung cancer	4.95	1.29-19.0	0.0196
Cervical cancer	6.36	1.74-23.2	0.0051

cemia was present in 10 (6.3%) participants. Regarding gastrointestinal disorders, gastric polyp was present in 675 (10.2%), colon polyp was present in 704 (10.6%), gallbladder polyp was present in 261 (3.9%), gallbladder stone disease was present in 231 (3.5%), and pancreatitis was present in 23 (0.3%) participants. In the pancreatic cyst indication group, gastric polyp was present in 20 (12.7%), colon polyp was present in 24 (15.2%), gallbladder polyp was present in 43 (27.2%), gallbladder stone was present in 8 (5.1%), and pancreatitis was present in 1 (0.6%) participant.

Regarding cancers, among all examinees (Table 2), gastric cancer was present in 55 (0.8%), colon cancer was present in 73 (1.1%), liver cancer was present in 4 (0.1%), biliary tract cancer was present in 3 (0.1%), lung cancer was present in 20 (0.3%), prostate cancer was present in 78 (2.0%), breast cancer was present in 96 (3.7%), and uterine/ovarian cancer was present in 40 (1.6%) participants. In the pancreatic cyst group, gastric cancer was present in 5 (3.2%), colorectal can-

cer was present in 3 (1.9%), lung cancer was present in 3 (1.9%), breast cancer was present in 2 (2.0%), and uterine/ovarian cancer was present in 3 (3.0%) participants; there were no cases of liver, biliary tract, and prostate cancer. All three cases of uterine/ovarian cancer in the pancreatic cyst group were cervical cancer.

On performing multivariate analysis using name logistic analysis, the factors associated with comorbidities of pancreatic cysts were found to be female sex (odds ratio 3.26,  $p < 0.0001$ ), age > 60 years (odds ratio 3.06,  $p < 0.0001$ ), diabetes (odds ratio 2.29,  $p = 0.0008$ ), lung cancer (odds ratio 4.95,  $p = 0.0196$ ), and uterine/ovarian cancer (odds ratio 6.36,  $p = 0.0051$ ) (Table 3-5).

**DISCUSSION**

In this study, five factors related to comorbidities of pancreatic cysts were identified: female sex, age > 60 years, diabetes, lung cancer, and uterine/ovarian cancer. Of these, age and diabetes were the same as those

previously reported. Regarding sex, more cases have been reported in men; however, in recent years, an equal number of cases have been reported in women, as in this study [8].

Regarding the complications of other organ cancers, pancreatic cysts are often associated with other organ cancers, and it has been reported that 20%-30% of the cases are concomitant or metachronous [9, 10]. Breast and prostate cancers are more common in Europe and the United States, while gastrointestinal cancers are more common in Asia [11, 12].

Certain genetic mutations are thought to be involved in pancreatic cysts and cancer complications. In pancreatic cancer, mutations in genes such as *KRAS*, *BNAS*, *SMAD4*, and *BRAF* are observed during carcinogenesis; *KRAS* gene mutations have been reported at a high rate of 60%, especially in carcinogenesis from pancreatic cysts [13]. The *KRAS* gene mutation is common in adenocarcinoma and is found in 15% of lung adenocarcinoma cases [14]. In this study, 3 cases of cervical cancer were found in the pancreatic cysts. Generally, cervical cancer has histological types of squamous cell carcinoma, but reports of adenocarcinoma cases are increasing in Japan. It has been reported that cervical cancer, which is a histological type of cancer, has a high rate of *KRAS* gene mutations in 17.5% [15].

From the results of this study, we concluded that chest imaging and gynecological examination may be considered when treating pancreatic cysts. In addition, when following up with patients having lung cancer and uterine/ovarian cancer, it may be considered to regularly perform imaging that can be used to scrutinize the pancreas. In ordinary medical care, scrutiny of comorbidities is limited by the burden on the individual and the medical economy, but it is possible to supplement, to some extent, by combining examinations in medical checkup screenings. We thought that it would be useful in terms of the adherence of the examinees and the early detection of comorbidities.

As a limitation of this study, since this study is limited to a small number of cases, it is hoped that more cases will be accumulated. In addition, except for the hospital chart for each individual's disease item, the presence or absence of morbidity is based on self-reports, and may differ from the actual morbidity.

## CONCLUSIONS

It is known that pancreatic cysts have a high complication rate in cancers of other organs, mainly gastrointestinal cancer. However, in this study, lung cancer and cervical cancer were found to be high-risk factors instead of gastrointestinal cancer.

Chest radiography and gynecological examinations can also be performed during regular medical checkup screening, and following the pancreatic cyst findings with the medical checkup screening is also may be useful from the viewpoint of adherence of the examinees and early detection of comorbidities.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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