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Usefulness of CA 19–9 for pancreatic cancer screening in patients with new-onset diabetes

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ABSTRACT

Background: Generally, carbohydrate antigen 19–9 (CA 19–9) is not useful for screening pancreatic cancer in the asymptomatic general population. This study aimed to evaluate the utility of CA 19–9 level as a screening indicator of pancreatic cancer in asymptomatic patients with new-onset diabetes.
Methods: We retrospectively reviewed the medical records of patients who visited our health promotion center for health check-ups without cancer related symptoms from January 2005 to January 2014, and were newly diagnosed with diabetes mellitus (DM) within 2 years before their visit.
Results: Of the 5111 asymptomatic patients with new-onset DM (<2 years) selected for analyses, 87 (1.7%) eventually developed pancreatic cancer after the health check-up. In the subgroup of 322 patients with high total bilirubin levels (>1.7 mg/dL) at the screening time, 42 (73.7%) of 57 patients with high CA 19–9 levels (>37 IU/mL) had been diagnosed as pancreatic cancer during follow-up period and 12 (4.5%) of 265 patients with normal CA 19–9 levels had finally developed pancreatic cancer (OR = 16.3). In the subgroup of 4789 patients with normal bilirubin levels, pancreatic cancer had been detected in 20 (3.8%) of 522 patients with high CA 19–9 level, while only 13 (0.3%) in 4267 patients with normal CA 19.9 levels (OR = 12.6), respectively.
Conclusion: CA 19–9 levels after a diagnosis of new-onset DM could be a useful biomarker of pancreatic cancer, especially in patients with high serum bilirubin.

Introduction

The outcomes of conventional treatments for pancreatic cancer are disappointing because of the very aggressive and rapidly growing nature of pancreatic cancer. Patients with pancreatic cancer do not have specific symptoms until it reaches an advanced stage. Thus, most cases of pancreatic cancer are not diagnosed until tumors have reached an unresectable and incurable state. Therefore, an early screening tool for detecting pancreatic cancer is necessary. Many studies have reported that new-onset diabetes mellitus (DM) can be an early sign of pancreatic cancer, and that patients with newly diagnosed DM should be screened for pancreatic cancer [1,2]. Thus, we previously evaluated the utility of carbohydrate antigen 19–9 (CA 19–9) measurement as a screening tool for pancreatic cancer in patients with new onset DM without pancreatic cancer-related symptoms [3]. The results of that study revealed that abnormally high CA 19–9 levels (>37 mg/dL) in asymptomatic DM patients were significantly associated with pancreatic cancer [3]. However, that retrospective study had a key limitation in that bilirubin levels were also higher in the pancreatic cancer group than in the non-pancreatic cancer group, and that bilirubin was an independent risk factor for pancreatic cancer in regression analysis. Patients with high bilirubin levels can present with jaundice, which is inconsistent with the definition of asymptomatic DM. Additional analyses were needed to confirm the usefulness of CA 19–9 as a screening tool after adjusting for bilirubin levels. In this study, we aimed to evaluate the utility of CA 19–9 in asymptomatic new-onset diabetic patients (<2 years) as a screening test for pancreatic cancer.

Methods

We reviewed the medical records of patients who visited health promotion centers of two affiliated hospitals in Korea university (Ansan Hospital and Guro Hospital) for health check-ups from January 2005 to January 2014 and were diagnosed with DM within

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2 years before their visit. They underwent measurement of liver function test (LFT), serum tumor markers, including CA 19–9 and carcinoembryonic antigen (CEA), and abdominal sonography as a routine part of the health care program. Additional computed tomography scan or magnetic resonance imaging was taken at the discretion of the physician. We enrolled a total of 5111 asymptomatic patients with new onset DM (<2 years). Exclusion criteria were (1) patients with pancreatic cancer-specific symptoms, such as prominent jaundice, right upper quadrant abdominal pain, or severe weight loss, based on a self-reported questionnaire; (2) patients with pancreatic cancer confirmed prior to checking of CA 19–9 level; (3) patients with a history of other malignancies; and (4) type 1 diabetic patients. This study was approved by the Institutional Review Board of Korea University Medical Center (KUGH 14,308). Criteria for a diagnosis of DM included (1) fasting plasma glucose (FPG) ≥ 126 mg/dL or (2) random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia or hyperglycemic crisis, or 3) HbA1c ≥ 6.5% [4].

First, the patients were divided into two groups: pancreatic cancer group and non-pancreatic cancer group. We compared clinical characteristics between the two groups, such as age, gender, body mass index (BMI), smoking history, CA 19–9, CEA, liver function, fasting blood glucose, and HbA1c levels. Second, the patients were divided by CA 19–9 expression using an upper normal limit of 37 U/mL. We estimated the relative risk ratio for pancreatic cancer according to abnormal CA 19–9 level. Third, the patients were also divided into two groups according to the total bilirubin level: normal bilirubin group (≤1.7 mg/dL) and high bilirubin group (>1.7 mg/dL). The risk ratio for pancreatic cancer according to abnormal bilirubin level was evaluated.

Statistical analysis

Statistical analyses were performed using $\chi 2$ tests or Fisher's exact tests for comparisons of discrete variables and independent two-tailed *t* tests for comparisons of continuous variables. Analyses of pooled data were conducted using univariate and multivariate logistic regression models to compute the odds ratio (OR) with 95% confidence intervals (CIs) as an estimate of relative risk. Two-tailed *P* values <0.05 were considered statistically significant. In the area under ROC curve (AUC) analysis, sensitivity and specificity were evaluated according to the value of CA 19–9 level as a screening test for pancreatic cancer. The Kaplan-Meier survival analysis was used to evaluate pancreatic cancer incidence after health check-up according to abnormal CA 19–9 level and bilirubin level, and the cumulative incidence curve was determined. All statistical analyses were conducted using IBM SPSS software (Version 20.0; SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics of the enrolled patients

This study included a total of 5111 patients (3280 males and 1831 females; mean age, 60.3 years). Among them, 87 (1.7%) developed pancreatic cancer during the follow-up period. The pancreatic cancer group had significantly higher CA 19–9 levels than the non-pancreatic cancer group [median (interquartile range, IQR); 132.1 (80.7–212.3) U/mL vs 27.3 (15.1–47.4) U/mL, $P < 0.01$]. Also, total bilirubin was significantly higher in the pancreatic cancer group [median (IQR); 1.46 (0.61–3.04) mg/dL vs 0.60 (0.41–0.97) mg/dL, $P < 0.01$]. However, there were no significant differences in age, gender, BMI, smoking history, CEA, HbA1C, glucose, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) between the two groups. Detailed characteristics of the pancreatic cancer and non-pancreatic cancer groups are shown in Table 1.

Table 1
Clinical characteristics of diabetic patients with or without pancreatic cancer.

Characteristics	Pancreatic cancer group ($n = 87$)	Non-pancreatic cancer group ($n = 5024$)	*P* value
Male/female	42/45	2712/2312	0.320
Age (yr, mean ± SD)	64.8 ± 10.0	65.4 ± 11.4	0.700
BMI (kg/m^2, mean ± SD)	24.5 ± 2.0	24.9 ± 1.9	0.070
Smoking	12 (14%)	753 (15%)	0.790
CA 19-9 (median, IQR, U/mL)	132.1 (80.7–212.3)	27.3 (15.1–47.4)	**0.002**
CEA (median, IQR, U/mL)	2.2 (1.0–4.0)	1.7 (1.0–2.9)	0.710
HbA1c (%)	7.7±1.8	7.6±1.9	0.680
Fasting glucose (mg/dL)	173.5±62.3	156.2±62.4	0.060
Total bilirubin (median, IQR, mg/dL)	1.46 (0.61–3.04)	0.60 (0.41–0.97)	**0.001**
Direct bilirubin (median, IQR, mg/dL)	0.85 (0.23–1.85)	0.24 (0.16–0.62)	**0.004**
AST (mg/dL)	41.0±40.7	36.6±32.6	0.100
ALT (mg/dL)	45.2±47.0	35.2±39.0	0.150

DM: diabetes mellitus; BMI: body mass index; CA 19–9: carbohydrate antigen 19–9; CEA: carcinoembryonic antigen; IQR: interquartile range; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 2
Univariate and multivariate logistic regression analyses for the risk of pancreatic cancer.

	OR (95% CI)	*P* value
Univariate regression		
Age	0.966 (0.939–0.994)	0.700
CA 19–9	1.002 (1.002–1.003)	**<0.001**
CEA	1.000 (1.000–1.001)	0.176
BMI	0.926 (0.856–1.001)	0.052
Smoking	1.172 (0.559–2.457)	0.675
Bilirubin	1.280 (1.147–1.428)	**<0.001**
Multivariate regression		
CA 19–9	1.002 (1.001–1.003)	**<0.001**
Bilirubin	1.153 (1.045–1.272)	**0.004**

OR: odd ratio; CI: confidence interval; CA 19–9: carbohydrate antigen 19–9; CEA: carcinoembryonic antigen; BMI: body mass index.

Risk factors for pancreatic cancer

In univariate and multivariate logistic regression analyses, high levels of both CA 19–9 and bilirubin were associated with a significantly increased risk of pancreatic cancer (Table 2).

Incidence of pancreatic cancer in high CA 19–9 and high bilirubin

Pancreatic cancer had developed in 62 (10.7%) of 579 patients with high CA 19–9 levels during follow-up period; only 25 patients (0.6%) were diagnosed with pancreatic cancer among the 4532 patients with normal CA 19–9 levels. The OR was 19.4 (95% CI: 12.10 to 31.13; $P < 0.001$) (Fig. 1).

When the patients were divided into two groups according to bilirubin level by using an upper normal limit of 1.7 mg/dL, pancreatic cancer was found in 54 (16.8%) of 322 patients with elevated bilirubin level and 0.7% (33/4789) with normal bilirubin level. The OR was 24.3 (95% CI: 15.56 to 38.07; $P < 0.001$) (Fig. 2).

The cumulative incidence of pancreatic cancer in DM patients with high CA 19–9 was significantly higher than that with normal CA 19–9 level (Fig. 3A); high bilirubin level was also associated with higher incidence of pancreatic cancer (Fig. 3B). The mean period from the time point of detecting abnormal CA 19–9

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