


Synergistic Association of Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 on the Risk of Abnormal Glucose Regulation

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Purpose: Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are tumor-associated antigens. An increased serum level of CEA and CA19-9 separately has been reported in diabetes. In this study, we examined the composite effect of elevated serum levels of both CEA and CA19-9 on subjects with type 2 diabetes and prediabetes.

Patients and Methods: A total of 3568 adults who attended a health examination were enrolled into this cross-sectional study. Subjects were grouped into four groups according to the median serum CEA and CA19-9 levels.

Results: Subjects with high CEA and high CA19-9 levels had the highest proportions of diabetes (43.9%) and prediabetes (33.04%). There was a statistically significant trend in the proportion of diabetes across the four groups ($P < 0.001$). Multivariable logistic regression analysis revealed higher risks of type 2 diabetes in subjects with high CEA and low CA19-9 levels (odds ratio [OR] = 2.10, 95% confidence interval [CI]: 1.39–3.18, $P < 0.001$) and in those with high CA19-9 and low CEA levels (OR = 2.18, 95% CI: 1.42–3.34, $P < 0.001$) than in those with low CEA and low CA19-9 levels; among these four groups, the highest risk of type 2 diabetes was observed in subjects with high CEA and high CA19-9 levels (OR = 2.65, 95% CI: 1.81–3.88, $P < 0.001$). The risk of prediabetes was significantly higher only in subjects with high CEA and high CA19-9 levels compared to those with low CEA and low CA19-9 levels (OR = 1.32, 95% CI: 1.08–1.61, $P = 0.006$).

Conclusion: CEA and CA19-9 had a synergistic ability to increase the risk of type 2 diabetes and prediabetes.

Keywords: CA19-9, CEA, diabetes, prediabetes, tumor marker

Introduction

Diabetes mellitus is one of the major causes of reduced life expectancy worldwide.¹ The global prevalence of diabetes among adults was estimated to be 8.8% in 2017, and this number is expected to increase to 9.9% by 2045.² Type 2 diabetes, which accounts for over 90% of all patients with diabetes, may remain undiagnosed for years, leading to unchecked progress of complications because of gradual, asymptomatic onset.^{3,4} Almost half of all adults with diabetes are not diagnosed globally, and the proportion of undiagnosed diabetes is as high as 30–50% even in high-income countries.^{3,5} Screening for prediabetes and type 2 diabetes using an informal assessment of risk factors or validated tools in asymptomatic adults is recommended according to the available guidelines.^{6,7}

Tumor markers are used clinically for cancer screening and monitoring. Generally, carbohydrate antigen 19–9 (CA19-9) and carcinoembryonic antigen (CEA) have been

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recommended to monitor gastrointestinal cancers.⁸ Furthermore, elevation of these two tumor markers was also observed in a number of benign conditions, including aging,⁹ hypothyroidism,¹⁰ inflammation,¹¹ chronic kidney disease (CKD),¹² pancreatitis,¹³ pulmonary diseases,¹⁴ cigarette smoking,¹⁵ and hepatobiliary system diseases.¹⁶ CEA and CA19-9 have similar features in clinical and biological studies, including both being expressed in gastrointestinal tumors.^{17,18} According to *in vitro* studies, CEA and CA19-9 both function as intracellular adhesion molecules.^{19,20} In the clinic, the combination of CEA and CA19-9 has a higher diagnostic efficiency than either marker alone in esophageal and gastric cancer,²¹ and is useful for predicting survival after potentially curative surgery in patients with colorectal cancer.²²

Numerous studies have reported that circulating CA19-9 is elevated during hyperglycemia in patients with diabetes.^{23–32} CA19-9 levels were revealed to be associated with hemoglobin A1c (HbA1c) and fasting blood glucose and to be decreased after improvement of glycemic control.^{28,33} The mechanism of elevated serum CA19-9 in diabetic patients remains unclear. However, some studies reported associations between CA19-9 elevation, β -cell function and insulin resistance.^{27,31,32} In addition, circulating CEA has been reported to increase in patients with diabetes^{33–38} and was positively associated with HbA1c.^{38,39} CEA levels are also reported to be associated with insulin resistance.⁴⁰

An increased risk of diabetes was reported in patients with pancreatic cancer, accompanied by high CEA and CA19-9 levels.⁴¹ However, the effects of combined CEA and CA19-9 levels on abnormal glucose regulation have not been reported in subjects without established malignancy. We therefore hypothesized that there was a synergistic association of CEA and CA19-9 on abnormal glucose regulation.

Patients and Methods

Patients

The aim of this cross-sectional study was to investigate the synergistic association of CEA and CA19-9 on type 2 diabetes and prediabetes. We retrospectively collected the medical information of subjects who had undergone health examinations at the Health Management Center in Taichung Veterans General Hospital between March 2009 and February 2018. Several health examination programs were offered, and some of the programs included the detection of CEA and CA19-9.

The inclusion criteria were adults who had complete data for CA19-9 and CEA in the health examination program. The exclusion criteria were (1) type 1 diabetes, (2) a history of any malignancy, (3) current pregnancy, (4) current inflammatory lesions in the lung, (5) anemia with hemoglobin (Hb) < 11 g/dL, (6) CKD with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², (7) a history of hypothyroidism, (8) a history of colon diseases, including inflammatory bowel disease and colonic polyps, (9) a history of liver cirrhosis, (10) a history of gallstones, and (11) a history of pancreatic disease. Only the data for the first program were recorded for subjects who had undergone repeated health examinations (Figure 1). Anonymous demographic characteristics and laboratory data were obtained from the Health Management Center after delinking the identification code. The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital in Taichung, Taiwan, with a waiver for obtaining informed consent.

Assessment

Data obtained from medical records included age, sex, height, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), white blood cell count (WBC) with the percentage of neutrophils, Hb, HbA1c, plasma glucose, serum levels of CEA, CA19-9, alanine aminotransferase (ALT), uric acid, creatinine, calcium, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, total protein, albumin, and total bilirubin.

Blood samples for biochemical analyses were collected in the morning after an overnight fast. Glucose was detected using an oxidase–peroxidase method (Wako Diagnostics, Tokyo, Japan). HbA1c was measured using cation-exchange high-performance liquid chromatography (National Glycohemoglobin Standardization Program certified; G8, TOSOH, Tokyo, Japan). Hb and WBC with differential counts were detected using a commercial auto-analyzer (Sysmex SE-9000, Kobe, Japan). Biochemical analyses were performed using a photometric enzymatic method with a chemical analyzer (Hitachi 7600, Tokyo, Japan). CEA and CA19-9 were detected using an Elecsys 2010 (Roche Diagnostics, Penzberg, Germany) in an electrochemiluminescence immunoassay.

Body mass index (BMI) was calculated as weight (kg)/(height [m])², and eGFR was calculated as $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$ ($\times 0.742$ if female).⁴² The absolute neutrophil count (ANC) was calculated as WBC \times neutrophil percentage. Smokers were defined as subjects

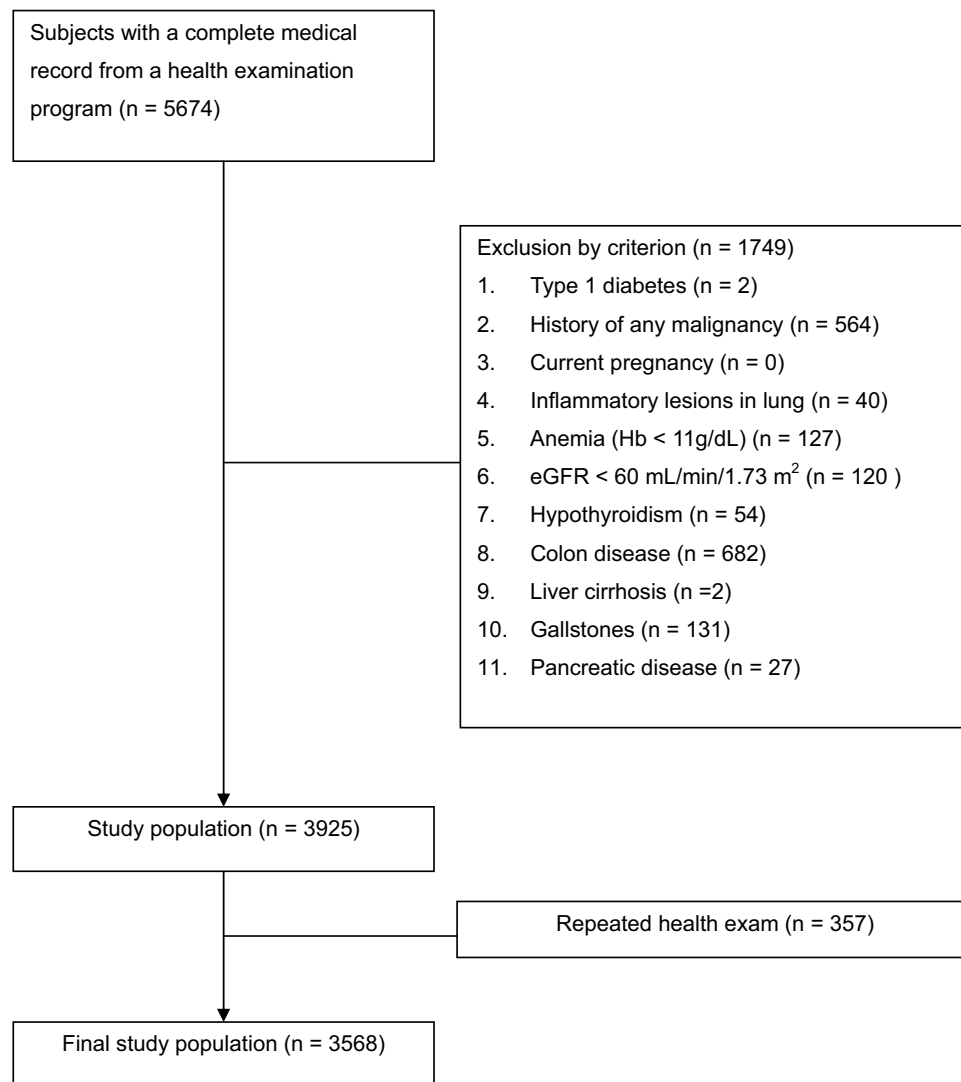


Figure 1 Flow diagram of the enrollment of study subjects.

Abbreviations: Hb, hemoglobin; eGFR, estimated glomerular filtration rate.

with a self-reported smoking history. Diabetes was defined according to a history of type 2 diabetes or use of antidiabetic drugs, an HbA1c level $\geq 6.5\%$, or a fasting glucose level ≥ 126 mg/dL in this health examination. Normal glucose was defined as no history of diabetes, HbA1c $\leq 5.6\%$, and glucose < 100 mg/dL in this health examination. Prediabetes was defined as an HbA1c between 5.7 and 6.4% or glucose between 100 and 125 mg/dL in subjects who did not meet the criteria for diabetes.⁷ Low HDL cholesterol was defined as an HDL < 40 mg/dL in men or < 50 mg/dL in women.⁴³

Statistical Analysis

All continuous data are presented as the median (interquartile range). The categorical data are presented as the number and percentage. A Mann–Whitney *U*-test was

conducted to detect significant differences in continuous variables between groups. Chi-square tests were conducted to detect differences in categorical variables. The correlation coefficient (ρ) and statistical significance of relationships were determined using Spearman correlation. Backward multivariate logistic regression was used to analyze the factors associated with type 2 diabetes and prediabetes. Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 3568 subjects were enrolled in the study, and their characteristics are shown in Table 1. To understand the influences of CEA and CA-199, we also showed the

Table 1 Clinical Characteristics of All Subjects, Grouped by a Median CEA of 1.75 Ng/mL and Grouped Based on a Median CA19-9 of 9.91 U/mL

Group	Total (n=3568)		CEA < 1.75 (n=1775)		CEA ≥ 1.75 (n=1793)		CA19-9 < 9.91 (n=1783)		CA19-9 ≥ 9.91 (n=1785)		P
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Diabetes	344	(9.64%)	114	(6.42%)	89	(82.94)	127	(7.12%)	217	(12.16%) ^{††}	<0.001
Prediabetes	1607	(45.04%)	733	(41.30%)	874	(48.75%) [†]	779	(43.69%)	828	(46.39%) [†]	<0.001
Normal glucose	1617	(45.32%)	928	(52.28%)	689	(38.43%)	877	(49.19%)	740	(41.46%)	<0.001
Glucose (mg/dL)	89	(83.96)	88	(82.94)	89	(84.98)	88	(82.94)	89	(83.98)	<0.001
HbA1c (%)	5.7	(5.4-5.9)	5.6	(5.4-5.9)	5.7	(5.5-6.0)	5.6	(5.4-5.9)	5.7	(5.5-6.0)	<0.001
Age (year)	50	(40-58)	47	(38-56)	53	(43-60)	48	(39-57)	51	(42-59)	<0.001
Male, n (%)	2003	(56.14%)	796	(44.85%)	1207	(67.32%)	1078	(60.46%)	925	(51.82%)	<0.001
Smoker, n (%)	981	(27.49%)	336	(18.93%)	645	(35.97%)	519	(29.11%)	462	(25.88%)	0.034
BMI (kg/m ²)	23.9	(21.5-26.0)	23.6	(21.3-26.0)	24.1	(21.8-26.5)	24.0	(21.7-26.5)	23.8	(21.3-26.2)	0.004
SBP (mmHg)	117	(106-129)	115	(104-126)	119	(107-131)	117	(105-128)	116	(106-130)	0.467
DBP (mmHg)	69	(62-78)	68	(62-76)	70	(63-79)	70	(62-78)	69	(62-78)	0.409
CEA (ng/mL)	1.75	(1.20-2.56)	1.20	(1.03-1.46)	2.55	(2.09-3.34)	1.54	(1.09-2.22)	1.96	(1.36-2.84)	<0.001
CA19-9 (U/mL)	9.91	(6.84-14.93)	8.93	(6.66-12.14)	11.63	(7.21-18.63)	6.84	(4.56-8.32)	14.92	(11.91-20.98)	<0.001
Hb (g/dL)	14.6	(13.5-15.7)	14.2	(13.2-15.4)	14.9	(13.8-16.0)	14.7	(13.5-15.7)	14.4	(13.4-15.7)	0.014
ANC (per μL)	3260	(2590-4115)	3226	(2559-4059)	3297	(2633-4163)	3277	(2617-4180)	3256	(2577-4057)	0.198
Total cholesterol (mg/dL)	195	(174-220)	193	(172-218)	197	(175-221)	194	(173-218)	197	(174-222)	0.032
HDL cholesterol (mg/dL)	51	(43-63)	52	(44-64)	51	(42-62)	51	(43-62)	52	(43-65)	0.008
Triglycerides (mg/dL)	105	(71-159)	100	(70-152)	112	(74-167)	103	(73-156)	107	(71-163)	0.368
ALT (U/L)	22	(16-32)	21	(15-31)	23	(17-34)	22	(16-32)	22	(16-33)	0.700
Total bilirubin (mg/dL)	0.9	(0.7-1.1)	0.9	(0.7-1.1)	0.9	(0.7-1.1)	0.9	(0.7-1.1)	0.9	(0.7-1.1)	0.798
Total protein (g/dL)	7.3	(7.0-7.6)	7.3	(7.1-7.6)	7.3	(7.1-7.5)	7.3	(7.1-7.6)	7.3	(7.0-7.6)	0.831
Albumin (g/dL)	4.5	(4.4-4.6)	4.5	(4.4-4.7)	4.5	(4.3-4.6)	4.5	(4.4-4.7)	4.5	(4.3-4.6)	0.012
eGFR (ml/min/1.73 m ²)	95.53	(85.10-108.31)	98.39	(86.87-110.90)	93.54	(83.50-105.55)	95.76	(85.54-107.8)	95.4	(84.75-109.01)	0.949
Uric acid (mg/dL)	5.9	(4.8-6.9)	5.7	(4.7-6.8)	6.00	(5.0-7.1)	6.0	(4.9-7.0)	5.7	(4.7-6.8)	<0.001
Calcium (mg/dL)	9.1	(8.8-9.3)	9.0	(8.8-9.3)	9.1	(8.8-9.3)	9.0	(8.8-9.3)	9.1	(8.8-9.3)	0.270

Notes: Data are expressed as median (interquartile range) or as n (%). Continuous data are expressed as medians (interquartile ranges); Categorical data are expressed as numbers (percentages). [†]indicates P < 0.001 compared with the normal glucose group; ^{††}indicates P < 0.001 compared with the prediabetes group.

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein (HDL); SBP, systolic blood pressure.

characteristics of all subjects grouped by a median CEA of 1.75 ng/mL and a median CA19-9 of 9.91 U/mL. A significantly higher proportion of diabetes was found in subjects with a high CEA level than in those with a low CEA level (12.83% vs 6.42%, $P < 0.001$), and a significantly higher proportion of prediabetes was found in subjects with a high CEA level than in those with a low CEA level (48.75% vs 41.30%, $P < 0.001$). Similarly, a significantly higher proportion of diabetes was found in subjects with a high CA19-9 level than in those with a low CA19-9 level (12.16% vs 7.12%, $P < 0.001$), and a significantly higher proportion of prediabetes was found in subjects with a high CA19-9 level than in those with a low CA19-9 level (46.39% vs 43.69%, $P < 0.001$).

A significantly higher glucose level (89 [84–98] vs 88 [82–94] mg/dL, $P < 0.001$) and a higher HbA1c level (5.7 [5.5–6.0] vs 5.6 [5.4–5.9] %, $P < 0.001$) were observed in subjects in the high CEA group than in the low CEA group; a significantly higher glucose level (89 [83–98] vs 88 [82–94] mg/dL, $P < 0.001$) and a higher HbA1c level (5.7 [5.5–6.0] vs 5.6 [5.4–5.9] %, $P < 0.001$) were observed in subjects in the high CA19-9 group than in the low CA19-9 group.

Furthermore, subjects in the high CEA group were older ($P < 0.001$) and had higher proportions of males ($P < 0.001$) and smokers ($P < 0.001$), a higher BMI ($P < 0.001$), a higher SBP ($P < 0.001$) and a higher DBP ($P < 0.001$), a higher Hb ($P < 0.001$), higher total cholesterol ($P = 0.006$), higher

triglycerides ($P < 0.001$), higher ALT ($P < 0.001$), higher bilirubin ($P < 0.001$), higher calcium ($P < 0.001$), higher uric acid ($P < 0.001$), lower HDL cholesterol ($P < 0.001$), lower total protein ($P < 0.001$), and lower eGFR ($P < 0.001$) than those in the low CEA group. There was no significant difference in ANC or serum albumin between these two groups.

Subjects in the high CA19-9 group were older ($P < 0.001$) and had lower proportions of males ($P < 0.001$) and smokers ($P = 0.034$), a lower BMI ($P = 0.004$), lower Hb ($P = 0.014$), higher total cholesterol ($P = 0.032$), higher HDL cholesterol ($P = 0.008$), lower uric acid ($P < 0.001$), and lower serum albumin ($P = 0.012$) than those in the low CA19-9 group. There was no significant difference in SBP, DBP, ANC, triglycerides, ALT, total protein, total bilirubin, calcium, or GFR between these two groups. It is notable that subjects in the high CEA group also had a higher CA-199 level (11.63 [7.21–18.63] vs 8.93 [6.66–12.14] U/mL, $P < 0.001$) and vice versa ($P < 0.001$). There was a significant positive correlation between CEA and CA19-9 levels ($\rho = 0.21$, $P < 0.001$).

To understand the synergistic association of CEA and CA19-9, we grouped all the subjects into four groups according to the medians of CEA and CA19-9: the high CEA with high CA19-9, high CEA with low CA19-9, low CEA with high CA19-9, and low CEA with low CA19-9 groups. The proportions of diabetes, prediabetes, and normal glucose among these four groups are shown in Figure 2. There were statistically significant differences in the proportions of diabetes, prediabetes and normal glucose across

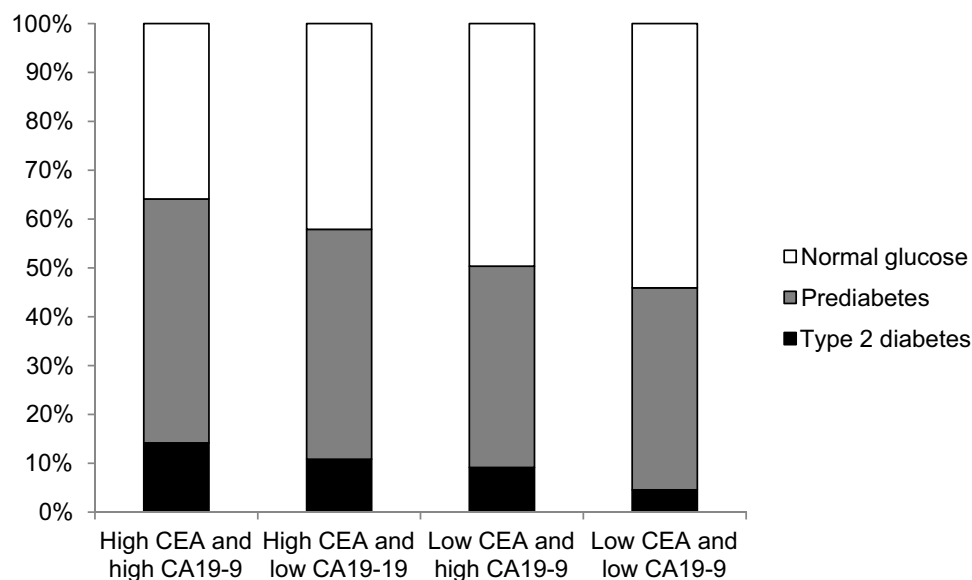


Figure 2 Proportions of type 2 diabetes, prediabetes and normal glucose among the four groups categorized according to median serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels; P values for trend < 0.001 for the proportions of diabetes, prediabetes and normal glucose.

these four groups (P values for trend were less than 0.001 for the proportions of diabetes, prediabetes and normal glucose). The high CEA with high CA19-9 group had the highest prevalence of diabetes, and there was a statistically significant trend for the prevalence of diabetes across these four groups (14.2%, 10.8%, 9.2%, and 4.6%, respectively; $P < 0.001$). In the subjects without diabetes, the high CEA with high CA19-9 group had the highest proportion of prediabetes and there was a statistically significant trend for the prevalence of prediabetes across these four groups (58.2%, 52.8%, 45.3%, and 43.3%, respectively; $P < 0.001$).

Using multivariate logistic regression analyses (Table 2), subjects with high CEA and low CA19-9 had a significantly higher risk of type 2 diabetes (odds ratio [OR] = 2.10, 95% confidence interval [CI]: 1.39–3.18, $P < 0.001$) than those with low CEA and low CA19-9. Similarly, subjects with high CA19-9 levels and low CEA levels had a significantly higher risk of type 2 diabetes (OR = 2.18, 95% CI: 1.42–3.34, $P < 0.001$) than those with low CEA levels and low CA19-9 levels. Furthermore, high CEA and high CA19-9 had a synergistic association, as demonstrated by the highest risk of type 2 diabetes (OR = 2.65, 95% CI: 1.81–3.88, $P < 0.001$) among the groups. On the other hand, subjects with high CEA and low CA19-9, or high CA19-9 and low CEA, did not have a significantly different risk of prediabetes compared with those with low CEA and low CA19-9 (OR = 1.19, 95% CI: 0.96–1.48, $P = 0.115$; OR = 1.12, 95% CI: 0.90–1.39, $P = 0.316$, respectively). However, subjects with high CEA and high CA19-9 had a significantly higher risk of prediabetes than those with low CEA and low CA19-9 (OR = 1.32, 95% CI: 1.08–1.61, $P = 0.006$).

Discussion

Our main finding in the present study is that subjects with high serum levels of both CEA and CA19-9 showed an increased risk of type 2 diabetes, compared to the increased level of just CEA alone or high CA19-9 alone. To the best of our knowledge, it is the first report that a combination of high CEA and CA19-9 levels was significantly associated with prediabetes, in spite of no significant association between prediabetes and high CEA alone or high CA19-9 alone. In previous studies, CEA was positively correlated with HbA1c only in patients with diabetes but not in subjects with prediabetes or normal glucose regulation.³⁹ Patients with new-onset diabetes had a higher risk of elevated CA19-9 levels than those with normal glucose after adjustments for confounders.³⁰

Because of the synergistic association of CEA and CA19-9 on the risk of type 2 diabetes or prediabetes, both tumor markers might play a pathophysiologic role in type 2 diabetes or prediabetes.

The mechanisms of CEA and CA19-9 in abnormal glucose regulation are still unclear. Hyperglycemia provides a potential condition for neoplastic proliferation. In vitro studies showed that a hyperglycemic environment stimulated the proliferation of breast and pancreatic cancer cells.^{44,45} In a mouse model, diabetes was associated with the development of skin and mammary tumors after tumor induction.⁴⁶ In a prospective study in the Vasterbotten Intervention Project in Sweden and in the Hong Kong diabetes registry study, hyperglycemia was reported to increase cancer risk.^{47,48} Poor glucose control has also been reported to be associated with a higher risk of all-cause mortality and recurrent cancer events in breast cancer survivors.⁴⁹

CEA induces the expression of inflammatory markers by activating monocytes and hepatic macrophages,⁵⁰ and subsequent inflammation might result in insulin resistance and the development of diabetes.^{51–54} CEA-related cell adhesion molecules play a role in neutrophil activation.⁵⁵ Chung et al³⁹ found that WBC and inflammatory markers showed positive correlations with both fasting glucose and HbA1c, and WBC was independently correlated with CEA in subjects with diabetes. Furthermore, insulin resistance with hyperinsulinemia might promote tumor cell proliferation via insulin-like growth factor receptors.^{56,57}

CA19-9 expressed by the exocrine pancreas is a marker of pancreatic tissue damage, which might be accompanied by impaired beta-cell function. Therefore, CA19-9 might reflect a decline in pancreatic function, including exocrine and endocrine functions. In addition, insulin insufficiency could result in pancreatic exocrine deficiency and release of CA19-9 by ductal cells.⁵⁸ Yu et al²⁷ demonstrated that increased serum CA19-9 levels were inversely correlated with pancreatic beta-cell function in patients with diabetes and claimed that long-term poor glycemic control may lead to beta-cell dysfunction, which is reflected by elevated serum CA19-9 levels. Therefore, an increase in serum CA19-9 levels might reflect the intensity of cellular dysfunction after metabolic disturbances. For patients with type 2 diabetes, the glucotoxicity generated by hyperglycemia is commonly thought to be the fundamental acquired factor that causes a continuous decline in beta-cell function in type 2 diabetes.^{59,60}

Table 2 Backward Multivariate Logistic Regression Analysis Showing Odds Ratios for Diabetes and Prediabetes Between Subjects with Different CEA and CA19-9 Levels

	Diabetes						Prediabetes					
	Univariate			Multivariate (backward)			Univariate			Multivariate (backward)		
	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
Group												
High CEA and high CA19-9	4.69	(3.31-6.66)	<0.001	2.65	(1.81-3.88)	<0.001	1.82	(1.52-2.18)	<0.001	1.32	(1.08-1.61)	0.006
High CEA and low CA19-9	3.06	(2.08-4.49)	<0.001	2.10	(1.39-3.18)	<0.001	1.46	(1.20-1.78)	<0.001	1.19	(0.96-1.48)	0.115
Low CEA and high CA19-9	2.19	(1.48-3.25)	<0.001	2.18	(1.42-3.34)	<0.001	1.08	(0.89-1.32)	0.422	1.12	(0.90-1.39)	0.316
Low CEA and low CA19-9	ref.			ref.			ref.			ref.		
Age (year)	1.11	(1.10-1.12)	<0.001	1.12	(1.11-1.14)	<0.001	1.06	(1.06-1.07)	<0.001	1.06	(1.05-1.07)	<0.001
Female (yes vs. no)	0.51	(0.40-0.65)	<0.001	0.56	(0.40-0.79)	0.001	0.74	(0.64-0.85)	<0.001	0.91	(0.74-1.11)	0.350
BMI (kg/m ²)	1.17	(1.14-1.21)	<0.001	1.15	(1.10-1.19)	<0.001	1.11	(1.09-1.13)	<0.001	1.07	(1.05-1.10)	<0.001
SBP (mmHg)	1.04	(1.03-1.04)	<0.001	1.01	(1.00-1.02)	0.046	1.02	(1.02-1.03)	<0.001	1.01	(1.00-1.01)	0.017
DBP (mmHg)	1.02	(1.01-1.03)	<0.001				1.02	(1.01-1.03)	<0.001			
Smoker (yes vs. no)	1.59	(1.24-2.04)	<0.001				1.17	(1.00-1.37)	0.048			
Hb (g/dL)	1.14	(1.05-1.23)	<0.001				1.09	(1.04-1.14)	<0.001			
ALT (U/L)	1.02	(1.01-1.02)	<0.001	1.01	(1.00-1.02)	<0.001	1.01	(1.01-1.02)	<0.001	1.01	(1.00-1.01)	0.001
Uric acid (mg/dL)	1.14	(1.05-1.23)	0.001	0.88	(0.79-0.98)	0.022	1.15	(1.10-1.20)	<0.001	0.97	(0.91-1.03)	0.330
Calcium (mg/dL)	1.53	(1.09-2.14)	0.014	3.03	(1.97-4.65)	<0.001	1.52	(1.24-1.86)	<0.001	2.09	(1.62-2.69)	<0.001
Total cholesterol (mg/dL)	1.00	(0.99-1.00)	0.019	0.99	(0.99-1.00)	0.001	1.01	(1.01-1.01)	<0.001	1.00	(1.00-1.01)	0.001
HDL cholesterol (normal vs. low) [†]	0.59	(0.45-0.76)	<0.001	0.80	(0.59-1.09)	0.151	0.67	(0.56-0.79)	<0.001	0.76	(0.63-0.92)	0.005
Triglycerides (high vs. normal) [‡]	2.02	(1.57-2.59)	<0.001				1.73	(1.48-2.03)	<0.001			
eGFR (ml/min/1.73 m ²)	0.99	(0.98-1.00)	0.004	1.02	(1.01-1.02)	<0.001	0.98	(0.98-0.99)	<0.001	1.00	(0.99-1.00)	0.182
ANC (per µL)	1.00	(1.00-1.00)	<0.001	1.00	(1.00-1.00)	<0.001	1.00	(1.00-1.00)	0.323	1.00	(1.00-1.00)	0.170
Total protein (g/dL)	0.67	(0.49-0.90)	0.009				0.82	(0.68-0.98)	0.025			
Albumin (g/dL)	0.43	(0.26-0.72)	0.001	1.10	(0.55-2.19)	0.792	0.47	(0.34-0.64)	<0.001	0.56	(0.37-0.83)	0.004
Total bilirubin (mg/dL)	0.83	(0.62-1.10)	0.200	0.61	(0.43-0.88)	0.007	0.92	(0.79-1.09)	0.339	0.84	(0.70-1.01)	0.068

Notes: All parameters in univariate logistic regression analysis were entered into the backward multivariate logistic regression analysis; ref, reference group; [†]Low HDL cholesterol was defined as an HDL < 40 mg/dL in men or < 50 mg/dL in women; others were normal HDL cholesterol; [‡]High triglycerides was defined as triglycerides ≥ 150 mg/dL; others were normal triglycerides.

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; BM, body weight index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein (HDL); OR, odds ratio; SBP, systolic blood pressure.

In addition to impaired beta-cell function, insulin resistance is a fundamental characteristic of type 2 diabetes. Esteghamati et al³¹ reported significant associations of CA19-9 with HbA1c and insulin resistance, and these associations were persistent in subjects with diabetes but not in those without diabetes. Tu et al³² found that insulin resistance is an important contributing factor in the changes in serum levels of CA19-9 after rapid metabolic control by Roux-en-Y gastric bypass. Since glucose toxicity is associated with insulin resistance and changes in the serum levels of CA19-9,⁶¹ the association between elevated CA19-9 and hyperglycemia might be involved in the mechanisms of both beta-cell dysfunction and insulin resistance.

Age, BMI, and blood pressure were shown to be independent risk factors for type 2 diabetes or prediabetes in the present study. These findings were in line with previous studies. Age is a major risk factor for type 2 diabetes, and the percentage of adults with diabetes increases with age.³ The risk of impaired glucose tolerance (IGT) or type 2 diabetes rises with increasing BMI.^{62–64} In addition, in a cohort investigation, hypertension were associated with an increased risk of developing type 2 diabetes.⁶⁵ Subjects with higher HDL cholesterol had a lower risk of prediabetes in the present study. Lower HDL levels are a characteristic of dyslipidemia in patients with type 2 diabetes. In the UK Prospective Diabetes Study (UKPDS), HDL cholesterol levels were reduced compared with those of the nondiabetic controls.⁶⁶

It is notable that calcium level was also an independent risk factor for type 2 diabetes or prediabetes in the present study. In a previous study, elevated serum calcium was found to be associated with a greater risk of type 2 diabetes.⁶⁷ This association remained significant even after adjustment for 25-hydroxyvitamin D, parathyroid hormone, and phosphate, which have themselves been associated with diabetes.^{68–70} However, eGFR was not an independent risk factor for prediabetes in this study. This nonsignificant result might be caused by excluding patients with CKD since they have higher CEA levels.¹²

This study had some limitations. First, we did not assess the causal effect of CEA and CA19-9 on abnormal glucose regulation in this cross-sectional study. Second, we did not assess the pathophysiological mechanism underlying the association between these tumor markers and diabetes. Third, our findings cannot be applied to patients with malignancy or disorders of the pancreas and colon because they were excluded from the present

study. Finally, there was no information on IGT since the oral glucose tolerance test was not included in the health examination program.

Conclusion

The present study found a synergistic association of CEA and CA19-9 on the risk of type 2 diabetes and prediabetes. This finding might provide a possible mechanism of CEA and CA19-9 in patients with type 2 diabetes and prediabetes. Further investigations to prospectively examine the causal effects of these tumor markers on diabetes and prediabetes are needed.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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