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RESEARCH ARTICLE

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HbA1c showed a positive association with carcinoembryonic antigen (CEA) level in only diabetes, not prediabetic or normal individuals

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Abstract

Background: This study was conducted to investigate the association of carcinoembryonic antigen (CEA) and glycated hemoglobin (HbA1c) in normal, prediabetic, and diabetic subjects.

Methods: A total of 2,911 participants who underwent general health checkups were enrolled and categorized into the normal, prediabetes, and diabetes groups. Demographic, anthropological, and clinical variables were investigated, and correlations with CEA were analyzed. For 28 diabetic subjects with CEA levels above the upper limit, the follow-up CEA and HbA1c data were analyzed.

Results: Carcinoembryonic antigen levels were significantly different among the normal, prediabetes, and diabetes groups (1.7 ± 1.1 vs 2.0 ± 1.1 vs 2.5 ± 1.5; $P < 0.001$), and men had higher CEA levels than women in all three groups. Correlation analysis identified a significant positive correlation between serum CEA and HbA1c in the diabetes group using unadjusted and adjusted models ($r = 0.189$, $P < 0.001$ and $r = 0.218$, $P < 0.001$), and multiple linear regression analysis also revealed that HbA1c was independently and positively correlated with CEA in the diabetes group ($\beta = 0.275$, $P < 0.001$). However, these relationships were inconsistent in the normal and prediabetes groups. The changes in CEA and HbA1c from baseline to follow-up (delta CEA and delta HbA1c) showed a significant positive correlation ($P = 0.021$).

Conclusions: In diabetes, the CEA level was independently and positively correlated with glycemic control status. Additionally, the change in CEA level (delta CEA) showed a positive correlation with the change in HbA1c level (delta HbA1c) in the follow-up data analysis.

KEYWORDS

carcinoembryonic antigen, diabetes, glycated hemoglobin

1 | INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer in males and ranks second in females, with 1.7 million new cases and almost 830, 000 deaths in 2016.[1] In recent years, diagnosis and treatment have progressed to a certain degree, but colorectal cancer is still a serious public health problem in the world. To guide decision-making for diagnosis and surveillance following the initial treatment for colorectal cancer, carcinoembryonic antigen (CEA) is widely utilized.[2,3]

Although serial measurements of CEA are widely recommended as part of a surveillance regimen in patients who underwent curative surgery for colorectal cancer, agreement is lacking among expert groups as to what constitutes clinically significant changes in CEA levels.[3] The National Academy of Clinical Biochemistry (NACB) presented a quality requirement guideline for the use of tumor markers, including CEA.[4] According to this guideline, the laboratory must exercise extra vigilance in ensuring that correct results are reported. Additionally, clinical conditions that might result in false elevation should be considered in the preanalytical phase. These clinical conditions include smoking,[5] hypothyroidism,[6] hypereosinophilia,[7] inflammatory bowel disease,[8] and diabetes.[9] Among those clinical conditions that might affect the level of CEA, diabetes is the most common chronic and metabolic disease. An estimated 285 million people worldwide had diabetes mellitus in 2010, and the number of people with diabetes will rise to 439 million by 2030, representing 7.7% of the total adult population of the world aged 20-79 years.[10] Furthermore, compared to non-diabetic subjects, diabetic patients are at increased risk of colorectal cancer[11] and show a lower 5-year overall survival rate when diagnosed with colorectal cancer, as demonstrated in a meta-analysis.[12]

Several studies have investigated the relationship between CEA levels and diabetes.[9,13,14] However, no studies have performed comprehensive medical checkups and screening, including endoscopic examinations, imaging studies, and wide-ranging blood tests including tumor markers and glycated hemoglobin, to rule out malignancy or other benign conditions that might affect CEA levels, as done in our health screening center, the Seoul National University Hospital (SNUH) Healthcare System Gangnam Center.[15] Furthermore, no study has showed the differences in CEA levels among normal, prediabetic, and diabetic individuals, or reported serial data on CEA levels associated with the glycemic control status in diabetic patients. Hence, in this study, we intended to identify the differences in CEA levels among normal, prediabetes, and diabetes groups and the extent of change in CEA levels according to levels of glycemic control in diabetic patients.

2 | METHODS

2.1 | Study population

The medical records of 25, 786 individuals who underwent opportunistic health checkups at the Seoul National University Hospital Healthcare System Gangnam Center from March 2015 to February 2016 were reviewed. Demographic characteristics and anthropometric measurements were acquired using medical questionnaires, nurse interviews, and health examinations during the health checkups.

The inclusion criteria were participants who completed the medical questionnaire and underwent general opportunistic health checkups, including laboratory and radiologic testing. The exclusion criteria were various medical conditions known to affect glycated hemoglobin and serum CEA levels, including thyroid function abnormalities, anemia, renal insufficiency, inflammatory bowel disease, colonic polyps, inflammatory lesions in lungs, or evidence of malignancy (Figure 1). Evidence of malignancy was based on radiologic findings, including esophagogastroduodenoscopy, colonoscopy, abdomen USG, low-dose chest CT, mammogram or breast ultrasonography, and on past medical history obtained using a medical questionnaire (Figure 1). Those who did not undergo esophagogastroduodenoscopy, colonoscopy, abdomen USG, low-dose chest CT, or mammogram/breast USG (female participants only) were also excluded. After application of the exclusion criteria, a total of 2,911 participants remained and were enrolled in this study.

2.2 | Demographic characteristics, anthropometric measurements, and laboratory data collection

A self-administered questionnaire was completed that included smoking history, alcohol ingestion, physical activity, antidiabetic medications, and underlying medical conditions such as malignancy and inflammatory disease. Alcohol ingestion and physical activity were defined as consumption of more than 20 g of alcohol per week and moderate intensity exercise for more than 150 minutes per week, respectively.

Blood sampling was performed after at least a 12-hour fast to evaluate the following: CEA, fasting blood sugar (FBS), HbA1c, TSH, leukocyte count, hemoglobin (Hb), and high-sensitivity C-reactive protein (hs-CRP). Serum was obtained from blood collected in a tube with a clot activator and serum gel separator, followed by centrifugation at 2,300 x *g* for 10 minutes within 30 minutes of blood draw to prevent glycolysis. Leukocyte count and Hb in EDTA-anticoagulated whole blood samples were analyzed using an ADVIA 2120 hematology analyzer (Siemens, Tarrytown, NY, USA). FBS and hs-CRP were measured using an Architect Ci8200 (Abbott Laboratories, Abbott Park, IL, USA). HbA1c was measured using an ADAMS HA 8160 analyzing system (ARKRAY Inc, Kyoto, Japan), which is a National Glycohemoglobin Standardization Program (NGSP)-certified method. CEA and TSH measurements were performed with a chemiluminescent microparticle immunoassay (CMIA) using i2000*sr* (Abbott Laboratories, Abbott Park, IL, USA). The laboratory-verified intra- and interassay variation coefficients were <2.9% and 3.1%, respectively. The reference interval for CEA provided by the manufacturer, 0.0-5.0 ng/mL, was used after validation following the Clinical and Laboratory Standards Institute guidelines (C28-A3).[16]

Diabetes was defined as an HbA1c level ≥ 6.5% or FBS level ≥ 126 mg/dL and/or antidiabetic medication use according to

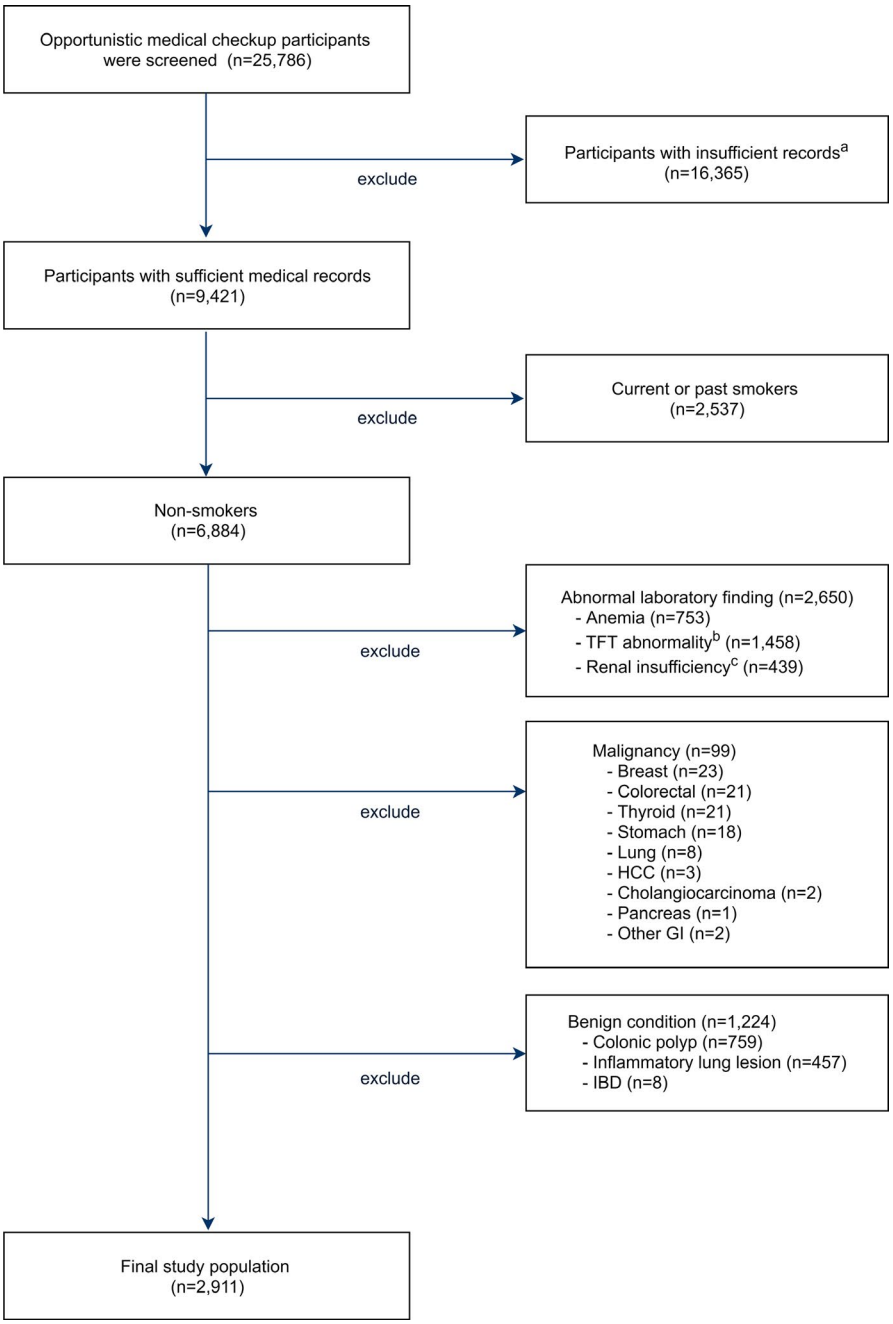

FIGURE 1 Flowchart of inclusion and exclusion criteria for the study. TFT, thyroid function test; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; GI, gastrointestinal. [a]Participants of both sexes without complete data on medical questionnaires, esophagogastroduodenoscopy, colonoscopy, abdomen CT, or low-dose chest CT. Female patients without complete mammogram/breast USG data and those lost to follow-up without further workup for final diagnosis. [b]Participants with TSH below 0.35 μIU/mL or above 4.94 μIU/mL. [c]Estimated glomerular filtration rate < 60 mL/min/1.73 m^2. MDRD GFR (mL/min/1.73 m^2) = 186 × SCr–1.154 × age-0.203 × 0.742 (in females), where SCr is serum creatinine

the diagnostic criteria set in the American Diabetes Association (ADA) 2012 guideline.[17] Prediabetes was defined as an HbA1c level ≥ 5.7% or a FBS level of 100-125 mg/dL without antidiabetic medication use. Normal was defined as an HbA1c level of <5.7% and a FBS level of <100 mg/dL without antidiabetic medication use. For the diabetic subjects with CEA levels above the upper limit of the manufacturer-provided reference interval (>5.0 ng/mL), follow-up CEA and HbA1c results were collected, and the changes between the follow-up and initial levels (delta CEA and delta HbA1c) were analyzed.

2.3 | Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD). Categorical variables were expressed as frequencies

or percentages. Person's chi-square test for categorical variables and analysis of variance (ANOVA) or independent t test for continuous variables were performed to assess differences among groups. Correlations between serum CEA levels and continuous variables, such as HbA1c, were determined by Pearson correlation coefficient (*r*) and Pearson partial correlation adjusted for age, sex, and BMI in all subjects and in the normal, prediabetes, or diabetes subgroup. Analysis of covariance (ANCOVA) was used to compare serum CEA levels according to alcohol ingestion or physical activity status after adjusting for age, sex, and BMI in the normal, prediabetes, or diabetes subgroup.

Additionally, we conducted multiple linear regression analyses using the stepwise method and enter method to evaluate the independent association between serum CEA level and HbA1c. Linear regression analysis adjusted for age and sex was performed to assess the relationship between delta HbA1c and delta CEA. A two-sided *P* value <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 22.0 for Windows (SPSS, Chicago, IL, USA) and MedCalc for Windows version 16.8.4.0 (MedCalc Software, Mariakerke, Belgium).

2.4 | Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (approval no. H-1606-013-770). Since the current study was performed as a retrospective study using the database and medical records, the requirement for informed consent was waived by the board.

3 | RESULTS

3.1 | General characteristics of the study population

A total of 2911 individuals (1,811 men and 1,100 women) were categorized into the diabetic group (n = 1,003), prediabetic group (n = 1,003), or normal group (n = 905) according to the ADA diagnostic criteria, and the characteristics of each group are shown in Table 1. A higher mean age, BMI, and male frequency were observed in the prediabetic and diabetic groups than in the normal group. The levels of CEA, FBS, HbA1c, leukocyte count, Hb, and hs-CRP showed significant differences among the three groups, with the lowest levels in the normal group and the highest levels in the diabetic group. More participants in the normal group than in the prediabetic or diabetic group performed moderate intensity exercise for more than 150 minutes per week. Participants with alcohol ingestion more than 20 g per week were more common in the diabetic group than in the normal or prediabetic group.

3.2 | Correlation of CEA levels with demographic and clinical characteristics of normal, prediabetic, and diabetic subjects

Correlation analysis identified a significant positive correlation between serum CEA and HbA1c in unadjusted and adjusted models among diabetic subjects ($r = 0.189$, $P < 0.001$ and $r = 0.218$, $P < 0.001$; Table 2). However, those relationships were not consistent among normal or prediabetic subjects. Hb levels showed a very weak correlation with CEA levels ($r = 0.065$, $P = 0.045$) among prediabetic subjects. FBS, HbA1c, leukocyte count, and Hb showed a positive correlation

TABLE 1 Characteristics and laboratory findings of the study subjects

Variables	Normal (n = 905)	Prediabetes (n = 1,003)	Diabetes (n = 1,003)	*P* Value[c]
Age, y	48 ± 11	59 ± 10	58 ± 10	<0.001
Sex, n (%)				
Men	416 (46.0%)	641 (63.9%)	754 (75.2%)	<0.001
Women	489 (54.0%)	362 (36.1%)	249 (24.8%)	
Alcohol ingestion[a]	517 (57.1%)	533 (53.1%)	600 (59.8%)	0.010
Physical activity[b]	348 (38.5%)	371 (37.0%)	306 (30.5%)	0.001
BMI	22.3 ± 3.0	24.2 ± 2.7	25.4 ± 3.3	<0.001
CEA	1.7 ± 1.1	2.0 ± 1.1	2.5 ± 1.5	<0.001
FBS, mg/dL	91 ± 5	108 ± 6	158 ± 36	<0.001
HbA1c, %	5.4 ± 0.1	6.0 ± 0.2	7.5 ± 1.1	<0.001
TSH, μIU/mL	1.73 ± 0.92	1.74 ± 0.98	1.74 ± 1.27	0.973
Leukocyte, × 10^3/μL	5.126 ± 1.354	5.489 ± 1.468	6.119 ± 1.647	<0.001
Hb, g/dL	14.1 ± 1.5	14.6 ± 1.2	14.9 ± 1.3	<0.001
hs-CRP, mg/dL	0.09 ± 0.22	0.12 ± 0.22	0.18 ± 0.45	<0.001

Values are presented as the mean ± standard deviation (SD) or number (percentage).
Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; FBS: fasting blood sugar; HbA1c, glycated hemoglobin; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone.
[a]Alcohol ingestion ≥ 20 g/wk.
[b]Moderate intensity exercise ≥ 150 min/wk.
[c]Comparison among normal, prediabetes, and diabetes participants.

TABLE 2 Association of serum CEA levels with demographic and clinical characteristics in the normal, prediabetes, and diabetes groups

	Normal				Prediabetes				Diabetes			
	Unadjusted*		Adjusted**		Unadjusted*		Adjusted**		Unadjusted*		Adjusted**	
Variables	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
Age	0.279	<0.001			0.175	<0.001			0.058	0.070		
BMI	0.139	<0.001			0.051	0.109			−0.019	0.545		
FBS, mg/dL	0.039	0.241	−0.052	0.123	0.059	0.060	0.025	0.437	0.234	<0.001	0.246	<0.001
HbA1c, %	0.020	0.555	−0.025	0.456	−0.015	0.643	−0.016	0.630	0.189	<0.001	0.218	<0.001
TSH, μIU/mL	−0.062	0.061	−0.072	0.033	0.032	0.311	0.015	0.652	−0.045	0.165	−0.039	0.232
Leukocyte, × 10^3/μL	0.078	0.020	0.060	0.075	0.090	0.005	0.073	0.024	0.185	<0.001	0.195	<0.001
Hb, g/dL	0.199	<0.001	0.060	0.075	0.090	0.004	0.065	0.045	0.164	<0.001	0.115	<0.001
hs-CRP, mg/dL	0.014	0.685	−0.025	0.456	−0.012	0.707	−0.027	0.411	−0.017	0.613	−0.003	0.938
	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value
Sex		<0.001				0.003				<0.001		
Male	2.0 ± 1.0				2.1 ± 1.1				2.6 ± 1.6			
Female	1.5 ± 1.0				1.9 ± 1.1				2.0 ± 1.2			
Alcohol ingestion		0.011		0.103		0.056		0.271		0.003		0.237
Yes	1.8 ± 1.1		1.8 ± 1.1		2.1 ± 1.2		2.1 ± 1.1		2.6 ± 1.6		2.6 ± 1.6	
No	1.6 ± 1.0		1.6 ± 0.9		1.9 ± 1.0		1.9 ± 1.0		2.3 ± 1.2		2.3 ± 1.2	
Physical activity		0.551		0.752		0.115		0.117		0.763		0.988
Yes	1.7 ± 1.0		1.7 ± 1.0		2.0 ± 1.1		1.9 ± 1.0		2.5 ± 1.5		2.5 ± 1.5	
No	1.7 ± 1.1		1.7 ± 1.0		2.1 ± 1.1		2.0 ± 1.1		2.5 ± 1.5		2.5 ± 1.5	

Abbreviation(s): BMI, body mass index; CEA, carcinoembryonic antigen; FBS: fasting blood sugar; HbA1c, glycated hemoglobin; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone; SD, standard deviation.

*Correlation coefficients (*r*) and *P* values were calculated using Pearson correlation analysis for continuous variables, and CEA levels were compared using the independent *t* test for categorical variables.

**Correlation coefficients (*r*) and *P* values were calculated by Pearson partial correlation for continuous variables, and CEA levels were compared by analysis of covariance for categorical variables after adjusting for age, sex, and body mass index.

TABLE 3 Multiple linear regression analysis of the factors affecting CEA levels in the normal, prediabetes, and diabetes groups

	Normal						Prediabetes						Diabetes					
	Stepwise method[a]			Enter method[b]			Stepwise method[c]			Enter method[b]			Stepwise method[d]			Enter method[b]		
Variables	*β*	SE	*P* Value	*β*	SE	*P* Value	*β*	SE	*P* Value	*β*	SE	*P* Value	*β*	SE	*P* Value	*β*	SE	*P* Value
Age	0.025	0.003	0.001	0.027	0.003	<0.001	0.021	0.004	0.001	0.022	0.004	<0.001	0.016	0.005	0.001	0.020	0.005	<0.001
Sex	0.409	0.068	<0.001	0.380	0.081	<0.001	0.299	0.074	<0.001	0.235	0.085	0.006	0.601	0.105	<0.001	0.478	0.119	<0.001
Alcohol ingestion[e]				0.139	0.073	0.057				0.096	0.079	0.229				0.190	0.109	0.081
Physical activity[f]				-0.023	0.068	0.732				-0.088	0.073	0.233				0.070	0.100	0.486
BMI				-0.010	0.013	0.429				0.018	0.013	0.180	-0.031	0.014	0.027	-0.027	0.014	0.056
HbA1c, %				-0.104	0.255	0.683				-0.104	0.177	0.558	0.275	0.041	<0.001	0.282	0.041	<0.001
TSH, μIU/mL	-0.081	0.036	0.024	-0.077	0.036	0.033				0.013	0.036	0.727				-0.040	0.037	0.276
Leukocyte, × 10^3/μL	0.051	0.025	0.041	0.059	0.027	0.025	0.059	0.025	0.017	0.066	0.026	0.011	0.162	0.029	<0.001	0.177	0.029	<0.001
hs-CRP, mg/dL				-0.019	0.157	0.903				0.235	0.085	0.186				-0.179	0.104	0.086

Adjusted R^2 = 0.128 (in enter method) and 0.129 (in stepwise method) in the normal group; adjusted R^2 = 0.054 (in enter method) and 0.109 (in stepwise method) in the prediabetes group; adjusted R^2 = 0.112 (in enter method) and 0.109 (in stepwise method) in the diabetes group.

Abbreviation(s): BMI, body mass index; CEA, carcinoembryonic antigen; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone.

In each analysis, model variables include

[a]age, sex, TSH, and leukocyte count

[b]age, sex, alcohol ingestion, physical activity, BMI, HbA1c, TSH, leukocyte count, and hs-CRP

[c]age, sex, and leukocyte count; and

[d]age, sex, BMI, HbA1c, and leukocyte count.

[e]Alcohol ingestion ≥ 20 g/week

[f]Moderate intensity exercise ≥ 150 min/wk.

TABLE 4 Stepwise multiple linear regression analysis of the factors affecting CEA levels in the diabetes group stratified by sex

	Males in diabetes group[a]			Females in diabetes group[b]		
Variables	***β***	**SE**	***P* value**	***β***	**SE**	***P* Value**
Age				0.042	0.007	<0.001
Alcohol ingestion[c]						
Physical activity[d]						
BMI	−0.055	0.018	0.003			
HbA1c, %	0.292	0.050	<0.001	0.212	0.061	0.001
TSH, μIU/mL						
Leukocyte, × 10^3/μL	0.174	0.035	<0.001	0.095	0.044	0.031
hs-CRP, mg/dL						

Adjusted R^2 = 0.087 (in male subjects) and 0.152 (in female subjects).
Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone.
In each diabetes subgroup, model variables include
[a]BMI, HbA1c, and leukocyte count; and
[b]age, HbA1c, and leukocyte count.
[c]Alcohol ingestion ≥ 20 g/wk.
[d]Moderate intensity exercise ≥ 150 min/wk.

with CEA levels (r = 0.246, P < 0.001; r = 0.218, P < 0.001; r = 0.195, P < 0.001; and r = 0.115, P < 0.001) among diabetic subjects. Male subjects had higher mean CEA levels than female participants in all three groups. Alcohol ingestion and physical activity did not show significant correlations with CEA levels in the adjusted model.

An independent association of CEA levels with HbA1c was assessed using multiple linear regression analysis (Table 3). Among diabetic subjects, the level of HbA1c was independently and positively correlated with the level of CEA in the stepwise-method analysis (β = 0.275, P < 0.001; adjusted R^2 = 0.109), and the association persisted in the enter-method analysis after adjusting for age, sex, alcohol ingestion, physical activity, BMI, TSH, leukocyte count, and hs-CRP (β = 0.282, P < 0.001; adjusted R^2 = 0.112). However, the significant relationship between CEA level and HbA1c was not consistent in the normal and prediabetes groups. In addition, age and sex showed significant associations with CEA levels in all subgroups, and BMI showed a negative correlation with CEA levels in only the diabetes group, not the prediabetes or normal group. Associations among alcohol ingestion, hs-CRP, and CEA levels in the total study population disappeared after grouping based on diabetic status (Table S1).

Since sex was strongly associated with CEA levels in the diabetic group, we performed multiple linear regression analysis among diabetic subjects stratified by sex. The independent association between CEA level and HbA1c was consistently shown in both male (β = 0.292, P < 0.001; adjusted R^2 = 0.087) and female diabetic subjects (β = 0.212, P < 0.001; adjusted R^2 = 0.152; Table 4).

3.3 | Change in CEA level according to the glycemic control status in the diabetes group

Among the 80 (8.0%) diabetic subjects with CEA levels above the upper limit of the manufacturer-provided reference interval (>5.0 ng/mL), 28 underwent follow-up CEA and HbA1c tests with a median follow-up period of 405 (358-719) days. A linear association between delta ("follow-up level" minus "initial level") CEA and delta HbA1c was shown after adjusting for age and sex (Figure 2). The equation describing the association between delta CEA and delta HbA1c was $y = 1.130 + 0.432x$, where x is delta HbA1c (%) and y is delta CEA (ng/mL) (P = 0.021).

4 | DISCUSSION

This study evaluated the association between CEA and HbA1c levels in normal, prediabetic, and diabetic subjects. Interestingly, the data showed that CEA levels in the prediabetes group were higher than those in the normal group and lower than those in the diabetes group. However, CEA level showed a positive correlation with HbA1c in only the diabetes group, not in the prediabetes or normal group. In a small follow-up group of 28 diabetic patients, the extent of the change in the CEA level was significantly correlated with the change in HbA1c, which reflects the relationship between glycemic control status and CEA level.

Although a clear mechanism for elevated CEA levels in diabetes has not yet been elucidated, there are a few hypotheses regarding this relationship. First, the association between CEA and HbA1c may be a sign of potential neoplastic proliferation in the hyperglycemic environment.[13] Diabetes increases the relative risks of cancer of the liver, pancreas, endometrium, colon and rectum, breast, and bladder.[18] Most cancer cells, including colorectal cancer cells, express insulin and insulin-like growth factor (IGF-1) receptors.[19] After these receptors bind their ligands, multiple signaling pathways, such as those involving the insulin receptor substrate (IRS) family, can be initiated, resulting in the stimulation of multiple cancer processes, including proliferation, invasion, and metastasis. Additionally, hyperglycemia allows IGF-I to stimulate vascular smooth muscle

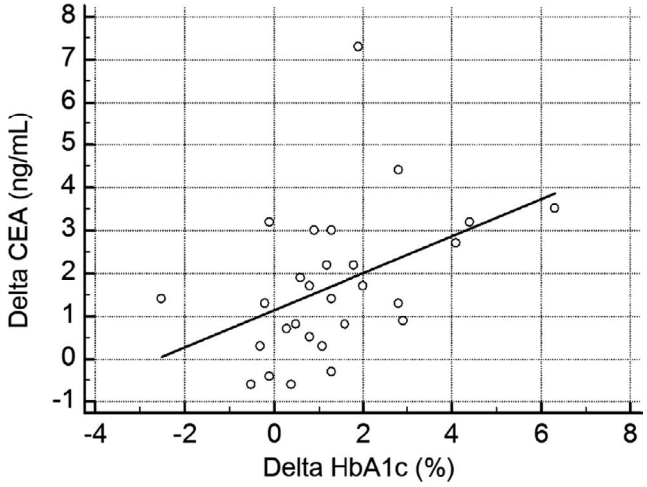

FIGURE 2 Association of delta ("follow-up level" minus "initial level") CEA with delta HbA1c in diabetic subjects (n = 28). The linear regression equation is $y = 1.130 + 0.432x$, where x is delta HbA1c (%) and y is delta CEA (ng/mL) ($P = 0.021$). Data were adjusted for age and sex. CEA, carcinoembryonic antigen; HbA1c, glycated hemoglobin

cell proliferation and migration, resulting in abnormal vasculature growth in cancer.[20] Surrogate markers of hyperinsulinemia, such as postprandial C-peptide and nonfasting insulin, are more strongly associated with colorectal cancer. [21]Increased circulating insulin might stimulate the growth of aberrant crypt foci and increase the number and size of tumors.[22] Other gastrointestinal tumor markers, such as CA 19-9, have also been reported to be elevated in diabetic patients and to have a positive correlation with HbA1c.[23] Although the mechanism underlying the positive correlation between CA 19-9 levels and HbA1c in diabetic patients remains unclear, the authors claimed that CA 19-9 might be released by exocrine pancreatic ductal cells damaged from glucose toxicity in poorly controlled diabetic patients.

In contrast to the hypothesis that this relationship between elevated CEA and poor glycemic control in diabetes promotes a neoplastic condition, there is some evidence that this relationship could be more benign. CEA might facilitate the production of inflammatory markers by activating monocytes and hepatic macrophages[24] and interact with CEA-related cell adhesion molecules (CEACAMs) to regulate neutrophil activation.[25] Patients with diabetes were reported to have increased levels of inflammatory molecules such as CRP, adiponectin, and interleukin-6 and a higher leukocyte count.[26-28] In this study, the leukocyte count and hs-CRP level showed a positive correlation with both FBS and HbA1c, supporting these findings ($0.12 <$ all $r < 0.24$, all $P < 0.001$; data not shown). In particular, leukocyte count was independently and positively related to CEA levels in all groups, and the β value was higher in diabetic subjects, indicating that leukocyte count had a greater influence on CEA in the diabetes group than in the other groups.

The associations among diabetes, metabolic syndrome, dyslipidemia, and cardiovascular disease (CVD) are well known: Diabetes mellitus is associated with an increased risk of CVD, and dyslipidemia is common in diabetes [29]; additionally, HbA1c was associated with subclinical cardiac alterations.[30] Although tight lipid control in diabetes is recommended to improve the cardiovascular outcomes, interestingly, dyslipidemia treated with lipophilic statin impairing mitochondrial function in pancreatic islets might have caused type 2 diabetes in reverse.[31,32] On the other hand, CEA levels were reported to be associated with metabolic syndrome and coronary artery disease.[33,34] Moreover, the lipid profiles have been reported to be significantly associated with colon cancer.[35] Considering those complex relationships, the mechanism for positive correlation between glycemic control and CEA might be more complicated than just hyperglycemia-induced carcinogenesis or inflammation, and we cannot exclude the probability that positive correlation between CEA and HbA1c is affected by possible confounding such as dyslipidemia or CVD.

In this study, we revealed the demographic and anthropometric parameters that are associated with CEA levels. Male sex and age showed positive correlations with CEA levels in all subgroups; however, the influence of age, reflected by β value in the multiple linear regression analysis, was much smaller than that of sex. BMI negatively affected CEA levels in only the diabetes group, not in the normal or prediabetes subgroup. Similar to our study, Lu et al reported that male diabetic patients had higher CEA levels than females, and obese diabetic patients had lower CEA levels than patients with a normal BMI.[9] We demonstrated that HbA1c is an independent factor that influences the level of CEA in subjects of both sexes with diabetes. Since we reviewed the medical records thoroughly and excluded other clinical conditions that might affect CEA levels, including smoking, the β value was significantly higher than that reported previously by Lu et al.[9]

According to the NACB guideline,[4] awareness of false elevations caused by benign clinical conditions is essential for proper interpretation. Furthermore, the patient's own "baseline" provides the most important reference point for the interpretation of marker results. Litvak et al followed patients who underwent resection for locoregional colorectal cancer and reported that false-positive or transient elevations of CEA are common in the range of 5 to 15 ng/mL;[36] however, the authors did not reveal the specific cause of this transient elevation. Although false elevation of CEA associated with diabetes has been noted,[9,13,14] the relationship between the extent of change in glycemic control status and CEA level had not been demonstrated before this study. Therefore, it is noteworthy that the follow-up level of CEA significantly decreased as HbA1c decreased with glycemic control, demonstrating the assumed effect of glycemic control on CEA levels, although this conclusion was based on data from a small number of follow-up subjects. In the future, following both CEA and HbA1c might help in the comprehensive interpretation of CEA levels considering glycemic control status, especially in diabetic colorectal cancer patients.

There are some limitations of this study. First, we could not perform an experiment to elucidate the clear mechanism connecting diabetes or increased HbA1c to CEA levels. Further studies may reveal the mechanisms of the interaction between endocrine

and/or exocrine pancreatic dysfunction and CEA levels in diabetes. Second, because the measurement method for CEA is not yet standardized,[37] the extent of change in CEA and HbA1c levels cannot be directly applied to other CEA measurement methods. Third, we could not obtain information about hypertension, dyslipidemia, CVD, or related medications, and thus were not able to investigate their influence on levels of CEA or HbA1c as we mentioned above. Fourth, the results cannot be directly applied to diabetic colorectal cancer patients under surveillance. Since all of our study participants completed comprehensive medical checkups and were considered negative for malignancy, we missed the lipid profiles that is related to colon cancer: Serum total cholesterol (TC) or high-density lipoprotein cholesterol (HDL-C) was significantly lower in colon cancer patients compared to those in healthy subjects, and the combination of TC, HDL-C, CEA, and CA 19-9 showed highest positive predictive value of colon cancer.[35] Fifth, we had follow-up data for only 28 out of the 80 diabetic subjects with a CEA level above the upper reference limit. However, delta HbA1c showed a significant correlation with delta CEA, and thus, longer follow-up studies will clarify this relationship. The future study with larger-scaled subjects, including diabetic dyslipidemia or CVD patients with treatment information, and colorectal cancer patients, will provide a comprehensive interpretation of their associations and will make the results applicable to cancer patients.

In conclusion, CEA levels are independently and positively correlated with HbA1c levels in diabetic patients. The change in the CEA level during follow-up showed a significant correlation with the change in the HbA1c level according to glycemic control. Our findings provide valid information on CEA levels in diabetic patients who have been diagnosed with or are undergoing monitoring for colorectal cancer. A similarly designed study performed in colorectal cancer patients with diabetes would provide practical guidelines for the interpretation of CEA levels in a specific patient population.

CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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