Research Article

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Influence of Obesity on the Serum Carcinoembryonic Antigen Value in Patients with Colorectal Cancer

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Abstract

Background: Prior studies suggest that obesity is inversely associated with tumor marker concentration and may reduce diagnostic precision. This study was undertaken to evaluate the association between body mass index (BMI) and serum carcinoembryonic antigen (CEA) concentrations in colorectal cancer patients.

Methods: We analyzed the association between BMI and CEA concentration in a group of 2,845 patients who underwent surgical treatment for colorectal adenocarcinoma from 1995 to 2009. Multivariate linear regression analysis was applied to adjust for clinicopathologic confounding factors to analyze main outcome measures. The association of BMI with plasma volume, CEA concentration, and total circulating CEA mass was assessed by determining *P* values for trends. We also developed a regression formula to calculate the effect of obesity on the serum CEA levels.

Results: Increased BMI was linearly correlated with higher plasma volume ($P < 0.001$ for trend) and lower adjusted CEA concentrations after controlling for potentially confounding factors ($P \leq 0.005$ for trend in stage II and III tumors). Our theoretical model suggests that a CEA value of 7.0 ng/mL in patients of normal weight corresponds to 6.1 ng/mL in obese patients.

Conclusions: The hemodilution effect from increased plasma volume may account for the decreased CEA concentrations observed in patients with higher BMI.

Impact: Obesity might be one of the factors that affect CEA value, leading to loss of sensitivity and diagnostic accuracy in the CEA test. The BMI status of patients should be taken into account during assessment of serum CEA during the surveillance of colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 19(10); 2461–8. ©2010 AACR.*

Introduction

Tumor markers have been commonly employed for several decades in routine clinical settings, including diagnosis, predicting prognosis, and monitoring the effects of treatment. Following the initial description and characterization in 1965 by Gold and Freedman, carcinoembryonic antigen (CEA) has been one of the most extensively investigated markers for colorectal cancer (1). Serial measurement of serum CEA facilitates the detection of recurrent disease with a sensitivity of 80% and specificity of 70%, providing a lead time of five months (2). Multiple studies additionally show that elevated preoperative CEA values are associated with more advanced disease and worse outcomes after surgical resection, independently of tumor stage and histologic grade (3-5).

Despite the widespread use of the CEA test, there are still some unresolved issues about its accuracy. As serum CEA concentration is affected by a variety of factors, clinicians often have difficulty in interpreting CEA results to assist in treatment decisions and in the design of follow-up strategies. Regarding specificity, CEA can be elevated in about 50% of epithelial tumors at other sites. Cigarette smoking is one of the well-known variables associated with increased CEA concentrations. Previous investigations showed that smoking seems to almost double the serum concentration of CEA (6, 7). Levels higher than normal have additionally been observed in individuals with cirrhosis, pancreatitis, uremia, and ulcerative colitis, whereas an inverse relationship between tumor grade of colon cancer and serum CEA concentrations has been reported (8-10).

Recent studies have examined the association between obesity and serum concentrations of soluble tumor markers. These studies showed that obese populations have lower tumor marker concentrations than do nonobese subjects (11, 12). It was suggested that the larger vascular volume of obese people caused a dilutional effect, a phenomenon known as hemodilution (13).

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Based on the above, we hypothesized that the diagnostic precision of the CEA test was affected by body mass index (BMI) status. This theory was examined in the context of colon cancer, and we explored whether large plasma volumes in obese patients were associated with lower CEA concentrations. In addition, the influence of BMI status on interpretation of preoperative CEA value was assessed in the clinical practice.

Materials and Methods

Patients

The collected records of 3,259 consecutive colorectal cancer patients from May 1995 to March 2009 were reviewed retrospectively. Analyses were confined to patients with BMI >16 kg/m^2, as lower values are likely to represent data errors or to reflect underlying disease processes. We excluded patients with missing BMI data (n = 53), no recorded preoperative CEA concentration (n = 20), and absence of pathologic staging (n = 38). Patients with a history of malignancy or inflammatory bowel disease (n = 150), renal insufficiency requiring hemodialysis or an advanced stage of liver cirrhosis (higher than Child's class B; n = 20), cancer of mucinous or squamous histology (n = 53), familial adenomatous polyposis (n = 51), or synchronous colon cancer (n = 29) were additionally excluded. The remaining 2,845 patients were included in the present analysis. Our local Institutional Review Board approved the survey before it was conducted.

Clinical variables

Preoperative BMI was calculated as weight in kilograms divided by height in meters squared. Height and weight were objectively measured using rigid stadiometers and digital clinical scales at admission. In view of the differences in the recommended BMI cutoff points for overweight status and obesity between Asian and western populations, the following categories were used: lower range of normal weight (BMI <20 kg/m^2), upper range of normal weight (BMI 20.0-22.9 kg/m^2), overweight (BMI 23.0-27.4 kg/m^2), and obese (BMI ≥27.5 kg/m^2; ref. 14).

Peripheral blood samples from colorectal cancer patients were obtained less than one week prior to operation. All baseline serum CEA concentrations were measured in a single laboratory at Kyungpook National University Hospital, with CEA concentrations >7.0 ng/mL regarded as "elevated" in our laboratory setting. Serum CEA was measured using a commercial RIA test kit (CEA-RIACT, CIS Bio International).

The estimated body surface area was calculated as (body weight)$^{0.425}$ × (height)$^{0.72}$ × 0.007184 (15). The estimated plasma volume (in liters) was calculated from body surface area as body surface area × 1.670 (16). CEA concentration was measured as ng/mL. CEA mass (in micrograms), representing the total amount of CEA protein within the circulation, was calculated as serum CEA concentration × estimated plasma volume.

All patients were monitored for more than five years or until death. Ultrasonography, computed tomography, serum CEA test, and chest X-ray examinations were done every 6 or 12 months. Additional histologic examination or imaging was done in patients with suspected tumor relapse to determine whether recurrence occurred. The criteria for establishment of recurrent disease included histologic confirmation, palpable disease, or radiologic evidence of disease with subsequent clinical progression and supportive biochemical data.

Statistical analysis

Data are given as mean (SD) and alternatively as median (interquartile range) according to normal distribution. Differences in the distribution of demographic and clinicopathologic characteristics between the groups (high CEA, >7.0 ng/mL versus low CEA, <7.0 ng/mL) were compared using the χ^2 test for categorical variables and the unpaired t-test or Mann-Whitney U test for continuous variables.

We used multivariate linear regression analysis (stepwise methods) to examine the relationship between BMI and CEA concentration. Variables were included in multivariate analysis if any P value was <0.20 in univariate analysis. Following the identification of independent confounding variables, adjusted CEA values were measured in regression model. We calculated values not exhibiting a normal distribution, such as serum CEA concentration, which were analyzed as continuous terms after logarithmic transformation and were subsequently back-transformed for the interpretation of model results. Trends between BMI category and CEA values were assessed with the χ^2 test for linear-by-linear association, and Spearman's rank correlation test.

Lastly, we developed a theoretical formula for estimating plasma CEA concentration in high-BMI patients corresponding to a reference value in normal-weight patients. We reconstructed the multiple regression model including BMI categories. Associations with $P < 0.05$ were considered statistically significant. All statistical analyses were done using SPSS software version 14.0 (SPSS Inc.).

Results

Data in the Kyungpook National University Hospital database, extracted from 2,845 patients who underwent the preoperative CEA test and met our study criteria, were analyzed. Mean age at surgery was 61.20 ± 11.04 years. Mean BMI and preoperative CEA concentration were 23.10 ± 3.0 kg/m^2 (range, 16.0-35.9) and 15.1 ± 100.9 ng/mL (range, 0-3,232), respectively. Enrolled patients were classified into BMI categories, based on redefined WHO criteria for the Asian Pacific region (14). Of all patients, 1,414 (49.7%) had normal BMI (BMI <22.9) and 1,430 (50.3%) were overweight or obese (BMI ≥23).

Table 1 compares demographic and clinicopathologic characteristics between patients with CEA <7 ng/mL

and ≥7 ng/mL. High-CEA patients tended to display a larger tumor diameter; a higher incidence of lymphatic, neural, and vascular invasion; a more advanced tumor-node-metastasis (TNM) stage; and a current history of smoking. Moreover, a significant difference in histologic tumor grade was observed between the two groups.

BMI, plasma volume, preadjusted and postadjusted CEA concentration, and CEA mass

Both BMI and plasma volume were calculated as functions of height and weight. Higher BMI was significantly associated with greater plasma volume (Table 2). Patients with BMI of ≥27.5 contained 10% to 15% larger plasma volumes relative to normal-weight patients. BMI correlated negatively with nonadjusted CEA concentration ($\gamma = -0.078$, $P < 0.001$). However, this trend across different BMI categories did not reach statistical significance upon reanalysis of this association according to TNM category. Next, we examined the association between BMI and CEA mass. The CEA mass did not change significantly with increasing BMI at any stage ($P = 0.627$, 0.440, 0.663, and 0.346 for trend across the four pathologic stages; Table 2).

Table 1. Analysis of demographic and clinicopathologic characteristics according to serum CEA level s in patients with colorectal cancer

Characteristics	CEA <7 ng/mL (*n* = 2,080)	CEA ≥7 ng/mL (*n* = 764)	*P*
Age at surgery in years, median (IQR)	63.0 (54.0-69.0)	62.0 (53.0-69.0)	0.131
Sex, no. (%)			0.178
Male	1,194 (55.4)	417 (54.6)	
Female	886 (42.6)	347 (45.4)	
ALT level (SD), IU/L	20.36 (14.69)	20.82 (18.74)	0.550
Smoking, no. (%)			<0.001
Current smoker	486 (23.4)	301 (39.4)	
Nonsmoker/Ex-smoker	1,594 (76.6)	463 (60.6)	
Tumor size in cm, median (IQR)	4.50 (3.0-6.0)	5.5 (4.5-7.0)	<0.001
Tumor location, no. (%)			0.086
Right side	480 (23.1)	200 (26.2)	
Left side	1,600 (76.9)	564 (73.8)	
Tumor grade, no. (%)			0.004
Well differentiated	283 (14.6)	70 (9.7)	
Moderately differentiated	1,572 (81.3)	620 (86.0)	
Poorly differentiated	79 (4.1)	31 (4.3)	
Bowel obstruction, no. (%)			<0.001
Presence	78 (3.8)	66 (8.6)	
Absence	2,002 (96.3)	698 (91.4)	
Bowel perforation, no. (%)			0.011
Presence	28 (1.3)	21 (2.7)	
Absence	2,052 (98.7)	743 (97.3)	
Lymphatic invasion, no. (%)			<0.001
Presence	835 (40.1)	435 (56.9)	
Absence	1,245 (59.9)	329 (43.1)	
Venous invasion, no. (%)			<0.001
Presence	87 (4.2)	62 (8.1)	
Absence	1,993 (95.8)	702 (91.9)	
Neural invasion, no. (%)			<0.001
Presence	589 (28.3)	333 (43.6)	
Absence	1,491 (71.7)	431 (56.4)	
Pathologic stage, no. (%)			<0.001
0/□	596 (28.6)	25 (3.3)	
□	702 (33.8)	233 (30.5)	
□	636 (30.6)	324 (42.4)	
□	146 (7.0)	182 (23.8)	

NOTE: Data presented as mean (SD) or median (IQR) according to normal distribution.
Abbreviations: ALT, alanine aminotransferase; IQR, interquartile range.

Table 2. Plasma volume and CEA mass by BMI category

	Stage	BMI category (kg/m^2)*				*P* for trend
		<20.0	20.0-23.0	23.0-27.5	>27.5	
Patients, no. (%)		446 (15.7)	968 (34.0)	1,206 (42.4)	224 (8.0)	
Plasma volume (SD), liters	0,I	2.39 (0.22)	2.59 (0.20)	2.73 (0.23)	2.86 (0.26)	<0.001
	II	2.42 (0.22)	2.61 (0.22)	2.74 (0.24)	2.90 (0.30)	<0.001
	III	2.46 (0.22)	2.59 (0.23)	2.75 (0.23)	2.88 (0.23)	<0.001
	IV	2.40 (0.26)	2.61 (0.21)	2.72 (0.23)	2.78 (0.18)	<0.001
CEA mass (IQR), μg	0,I	4.74 (3.11-6.62)	4.75 (3.33-7.41)	4.97 (3.07-7.85)	4.33 (2.20-2.28)	0.627
	II	8.84 (5.24-21.89)	7.46 (4.64-16.25)	7.03 (4.12-17.00)	10.23 (5.69-25.32)	0.440
	III	12.06 (5.39-41.83)	8.52 (4.49-26.78)	9.32 (4.95-23.16)	15.07 (5.21-36.08)	0.663
	IV	11.08 (5.70-60.77)	34.11 (7.71-112.38)	31.53 (7.05-99.95)	9.48 (3.32-233.97)	0.346

NOTE: Data presented as mean (SD) or median (IQR) according to normal distribution.
*Stratified by WHO recommendation for Asian population for international comparison.

Relationships among clinicopathologic variables were examined using multiple linear regression analysis. All analyses were mutually adjusted for potential confounding factors by including the following variables in the regression models: smoking (current smoker, nonsmoker/ex-smoker), tumor size (continuous), tumor grade (well, moderately, poorly differentiated), bowel obstruction (presence, absence), and neural invasion (presence, absence). After adjustment, higher BMI was inversely correlated with adjusted CEA concentration in stage I ($P = 0.142$ for trend), stage II ($P < 0.001$), and stage III ($P = 0.005$) disease (Fig. 1). Patients with BMI of ≥27.5 displayed 15% to 20% lower mean CEA concentrations relative to normal-weight patients. In stage IV cohorts, the adjusted CEA concentration was not significantly associated with BMI ($P = 0.503$).

Proportions of patients with abnormal CEA by each cutoff point

With 2.5 ng/mL as a cutoff, the frequencies of abnormal preoperative CEA for American Joint Committee on Cancer stages I, II, III, and IV were estimated as 31.9% (198 of 621), 57.9% (541 of 935), 64.2% (616 of 960), and 75.9% (249 of 328), respectively. At a 5 ng/mL cutoff value, these proportions were 8.1%, 32.4%, 42.0%, and 59.8% for stages I to IV, respectively. The proportions of patients with overall abnormal CEA at each cutoff value (2.5 and 5.0 ng/mL) decreased significantly with BMI (P for trend < 0.05 for both; Table 3). The same trend was also observed, but not statistically significant, between the proportion of patients with elevated CEA and BMI category using 7 ng/mL as the cutoff point (P for trend = 0.076).

Prognostic significance of preoperative CEA according to BMI

New or recurrent metastatic lesions following surgery developed in 469 (16.4%) patients. In the subgroup analysis for the recurrence cohort, we excluded patients with distant metastasis (stage IV). Next, we calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of preoperative CEA for tumor recurrence. Subgroup analyses included 209 obese (BMI >27.5 kg/m2) and 1,229 normal-weight (BMI <23 kg/m2) patients with a median follow-up period of 61 months (range, 1-181 months; Table 4). At a cutoff value of 2.5 ng/mL for preoperative CEA, sensitivities were estimated as 74.5% and 63.6% in the normal-weight and obese groups, respectively ($P < 0.001$). Specificity, PPV, and NPV were not significantly different between the two groups. At serum concentrations of >7.0 ng/mL (positive test), preoperative CEA concentrations were predicted with a sensitivity of 40.9%, specificity of 71.7%, PPV of 14.5%, and NPV of 91.2% in the obese group. Specificity and PPV were significantly lower in the obese group ($P < 0.05$).

Clinical interpretation of the influence of obesity on CEA concentrations

After determination of the relationship between BMI and CEA concentration, we investigated the impact of overweight status and obesity on this association, with a view to estimating the CEA concentration in high-BMI patients corresponding to a CEA of 7.0 ng/mL in normal-weight patients. We reconstructed the multiple regression model including BMI categories. The following formula was obtained upon statistical analysis: $\log_e$ [CEA] = 1.425 + 0.198 [stage] − 0.221 [differentiation] + 0.152 [neural invasion] − 0.070 [BMI]. In this mathematical model, each stage of colon cancer was given a point from 1 to 4 (i.e., stage I got point 1 and stage IV got point 4); each differentiation was given a point from 1 to 3 (i.e., well differentiation got point 1 and poor differentiation got point 3); each neural invasion was given point from 0 to 1 (i.e., neural invasion positive got point 1). Based on this theoretical formula, the observed CEA concentration

of 7.0 ng/mL in normal-weight patients corresponded to 6.1 ng/mL in obese patients.

Discussion

Accumulating epidemiologic evidence suggests that obesity is associated with cancer, particularly cancer of the colorectum. Recent consensus panels cite "convincing" evidence for obesity as a cause of colorectal cancer, but very few studies have to date considered the effects of obesity on serum tumor marker concentrations (17, 18). The results of the current study show that serum CEA concentrations are affected by obesity. The trends of decreasing CEA concentrations with increasing BMI category were similar to data from analyses stratified by tumor stage, which displayed a stronger linear association after adjustment for potentially confounding factors.

In the current study, we estimated CEA mass, which denotes the total amount of CEA protein in the blood at the time of determination of serum CEA concentration. Our data show that obese patients exhibited higher plasma volumes, but not CEA mass. Obese patients had similar or slightly higher CEA mass. These results corroborate the obesity-related hemodilution theory, stating that because there is no evidence that the concentration of the tumor marker in the circulation is regulated, the fixed amount of the tumor marker released from the tumor should be diluted into lower concentrations in patients with larger plasma volumes (19-21). Indeed, several small-scale reports suggest that changes in plasma volume influence the concentrations of tumor markers after hemodialysis or transplantation (22, 23).

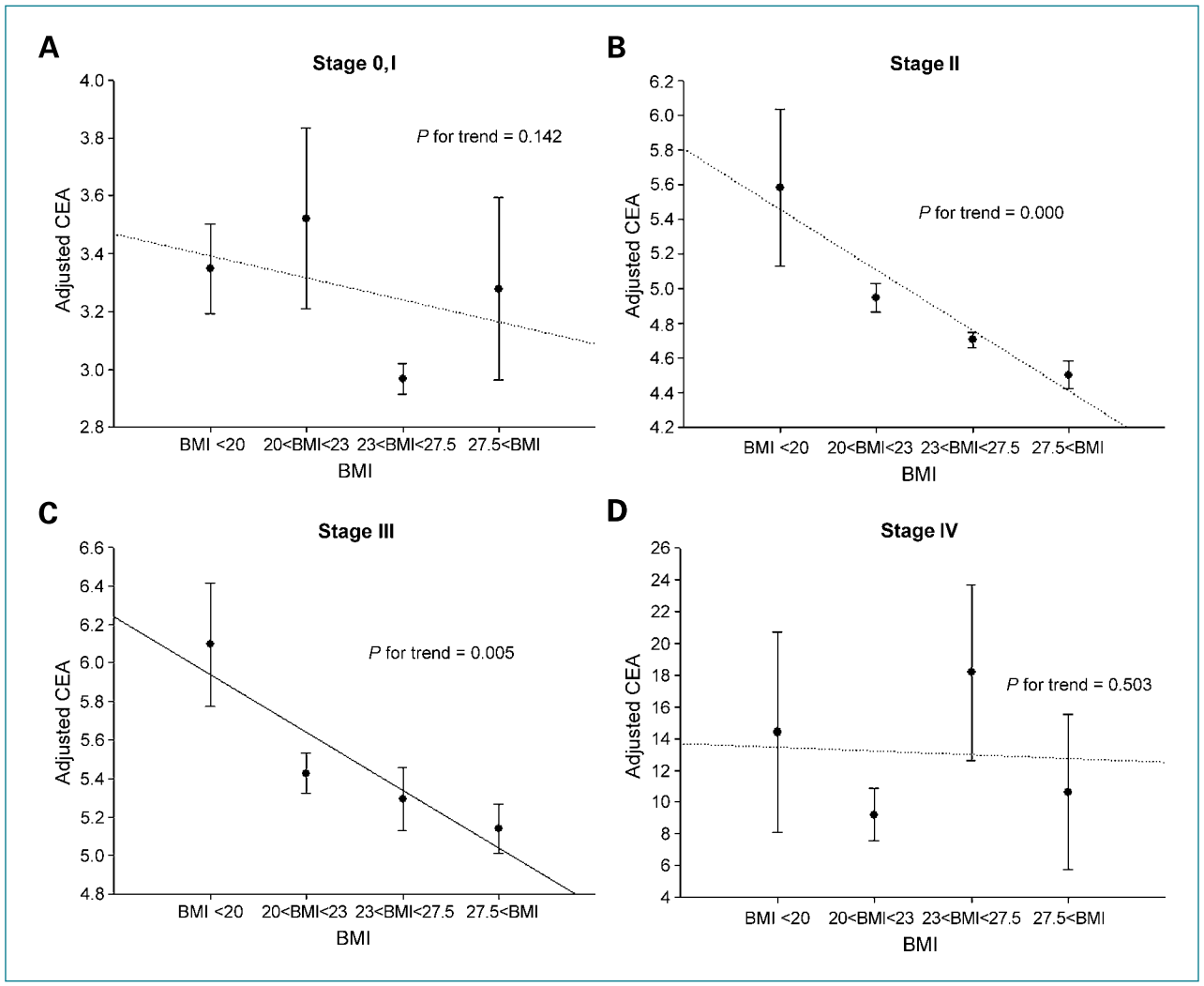

Figure 1. Mean adjusted concentrations of CEA according to BMI at stage 0-I (A), stage II (B), stage III (C), and stage IV (D). Analyses were all mutually controlled for independent confounding factors by including the following variables in the regression model: stage (categorical), smoking (categorical), tumor size (continuous), differentiation (categorical), bowel obstruction (categorical), and neural invasion (categorical).

Table 3. Proportion of patients with elevated CEA concentration by three different cutoff points according to BMI

		BMI category (kg/m^2)*				*P* for Trend
		<20.0 (*n* = 446)	20.0-23.0 (*n* = 968)	23.0-27.5 (*n* = 1,206)	>27.5 (*n* = 224)	
CEA cutoff value, (ng/mL)	>2.5	284 (63.7)	565 (58.4)	638 (52.9)	117 (52.2)	<0.001
	>5.0	174 (39.0)	336 (34.7)	362 (30.0)	80 (35.7)	0.008
	>7.0	134 (30.0)	274 (28.3)	289 (24.0)	67 (29.9)	0.076

NOTE: Data in parentheses are percentages.
*Stratified by WHO recommendation for Asian population for international comparison.

Our findings are consistent with prior population-based studies showing that obese men have a lower tumor marker concentration than do those of normal weight. In the present study, subjects in the most obese group displayed 15% to 20% lower serum CEA concentrations than normal-weight patients, in line with the 3.8% to 6.2% decrease in the CEA concentration reported in a population-based study of healthy men (11). In the cited study, an approximate 10% decrease in the concentration of another tumor marker, carbohydrate antigen 19-9, was reported, depending on plasma volume (11). The cited study differed from the present experiments in that the prior investigation was not community based and data were collected from patients undergoing routine heath screening. Furthermore, the prior study did not include populations with a wide range of CEA levels, as those with CEA values of >5.0 ng/mL were excluded from analysis. Accordingly, the mean adjusted CEA and the magnitude of the hemodilution effect were both slightly lower in the previous cohort.

The choice of the cutoff value is of great importance when interpreting the results. Although CEA >7.0 ng/mL is considered abnormal with our CEA assay systems, the cutoff value for "positive test" varies between institutions, from 3 to 15 ng/mL (24). Most prior studies used 5 ng/mL as the cutoff, but some authors have proposed a lower optimum value. In a previous study, the ideal CEA value was evaluated using receiver operating characteristic curve analysis, and the authors proposed that a cutoff of 4.0 ng/mL may provide an ideal balance of sensitivity and specificity (25). Tan and colleagues additionally carried out a quantitative meta-analysis of 20 previous studies. The optimum CEA value for maximizing diagnostic yield was 2.2 ng/mL in the cited work, with derived sensitivity and specificity values of 0.84 (24). In view of these reports, we selected multiple cutoff values to assess the effects of BMI on interpretation of CEA. Furthermore, our data suggest that upon lowering of the cutoff point, the sensitivity of the CEA test is affected to a greater extent as BMI rises.

Although most patients do not display elevation of CEA at the time of diagnosis, patient prognosis and preoperative CEA are correlated. The production and secretion of CEA by tumor cells has been described as a linear relationship between cell number and serum CEA value,

Table 4. Sensitivity, specificity, positive predictive value, and negative predictive value of high preoperative serum CEA for recurrence

CEA cutoff value (ng/mL)	Normal (*n* = 1,229) BMI <23 (kg/m^2)	Obese (*n* = 209) BMI >27.5 (kg/m^2)	*P*
Low, >2.5			
Sensitivity	146/196 (74.5)	14/22 (63.6)	<0.001
Specificity	471/1,033 (45.6)	93/187 (49.7)	0.335
PPV	146/708 (20.6)	14/108 (13.0)	0.082
NPV	471/521 (90.4)	93/101 (92.1)	0.731
High, >7.0			
Sensitivity	83/196 (42.3)	9/22 (40.9)	0.922
Specificity	814/1033 (78.8)	134/187 (71.7)	0.039
PPV	83/302 (27.5)	9/62 (14.5)	0.048
NPV	814/927 (87.8)	134/147 (91.2)	0.301

NOTE: Data in parentheses are percentages.

and, consequently, a preoperative CEA may aid in detecting patients at high risk of recurrence (26, 27). Preoperative CEA measurement may facilitate identification of a subset of patients with aggressive disease who could benefit from more active adjuvant therapy, particularly patients classified with stage II or stage III disease (27, 28). Recently, we reported that high preoperative serum CEA is an independent prognostic factor for tumor recurrence (29). In patients with high preoperative serum CEA, CEA surveillance showed 67.9% sensitivity, 96.1% specificity, a 92.3% PPV, and a 96.1% NPV for tumor recurrence (29). These findings, as well as the results of the current study showing that increased BMI negatively affects the diagnostic precision of the CEA test, pose an important query as to whether the measurement of preoperative CEA is less useful in obese patients. In cancer relapse patients, the sensitivity, specificity, and PPV of preoperative CEA at each cutoff point (2.5 or 7.0 ng/mL) was significantly reduced in the obese group. To effectively apply preoperative CEA measurement as a useful surveillance tool for tumor recurrence, it may be necessary to interpret the CEA concentrations of obese patients in a manner distinct from that of normal-weight patients.

We developed a theoretical formula to assess CEA concentration in relation to body size category for predicting the practical influence of obesity-related hemodilution on the interpretation of the serum CEA test. This model was used to estimate CEA values in overweight and obese patients corresponding to a CEA value of 7.0 ng/mL (the reference value of our laboratory) in normal-weight patients. Our model suggests that serum CEA of 6.1 ng/mL in obese patients and 6.5 ng/mL in overweight patients are mathematically equivalent to 7.0 ng/mL in normal-weight patients. The diagnostic accuracy of the CEA test may thus be improved by setting the reference value of the obese group about 10% to 15% lower than that of the normal-weight group.

In the present study, inclusion criteria were strictly applied and potentially confounding factors were adjusted to strengthen the validity of the results. Patients with chronic liver disease, renal insufficiency, mucinous histology, or inflammatory bowel conditions were excluded, as it was difficult to control for the effects of these factors on serum CEA concentration. Because our goal was to study the relationship of BMI and CEA independent of any association between BMI and colorectal cancer severity, all analyses were mutually adjusted for potential confounding factors. Multivariate linear regression analysis was then done to adjust for the effects of other variables (i.e., smoking) on CEA concentration. Comparison of the concentration of crude CEA with that after adjustment revealed that the strength of association between CEA concentration and BMI increased following adjustment. Another interesting finding was the lack of a significant relationship between obesity and CEA concentration in stage IV patients. We propose that the present regression model is insufficient to control for the contribution of distant disease as the formula does not include the quantitative volume of metastatic cancer deposits.

Nonetheless, we also assume that all the proinflammatory conditions affecting serum CEA levels did not seem to be completely controlled. The importance of chronic inflammation in the pathogenesis of obesity has been recently highlighted and may represent an additional mechanism linking increased adiposity to colorectal carcinogenesis. Hence, it is biologically plausible that serum CEA levels may be higher due to the elevated levels of a circulating inflammation-associated mediator in obese patients. Therefore, the negative association between obesity and serum CEA levels might be further pronounced in a certain group of obese individuals if the general impact due to obesity itself was also controlled. We did not collect inflammatory-related mediator levels in all of the patients in the cohort to test this hypothesis. Further prospective research is necessary to confirm that general inflammation resulting from obesity would affect the concentration of serum CEA.

In 2003-2004, 39.7% of U.S men were overweight (BMI $\geq$25 to <30 kg/m^2) and 31.1% were obese (BMI $\geq$30 kg/m^2; ref. 30). The mean BMI in previous reports evaluating the relationship between BMI and tumor marker concentrations in western populations was reported as 27.8 kg/m^2 to 28.1 kg/m^2 (21, 31). In contrast, the mean BMI in the present study was 23.4 kg/m^2, and the proportions of overweight and obese men were 24.9.0% and 2.0%, respectively. The proportion of obese subjects in the present study was less than one tenth that among western countries. Therefore, we employed the WHO BMI recommendations for Asian populations, to permit international comparisons (14). There were few obese patients in the present analysis, based on the conventional WHO standard, and the hemodilution effect of extreme obesity, particularly in western populations, may be more significant than shown in the current study.

Our study has several limitations. First, plasma volume was estimated using weight and height in the current study. There are other indicators that could provide more accurate prediction of plasma volume status and sequestration of tumor marker. For example, algorithms using lean body mass and hematocrit used for plasmapheresis may be arguably more ideal (32). However, we consider that estimation of plasma volume using body surface area is more acceptable in clinical practice. Second, we did not analyze the relationship between BMI and sensitivity of CEA during the postoperative surveillance because our database did not include the individual weight change after surgical treatment. Based on our results, it is inferred that the larger proportion of the obese cohort may be likely to have the normal value of CEA than that of the standard-weight group in spite of the disease recurrence. The additional prospective investigation on the relationship of obesity and CEA should be followed because obesity may result in delayed cancer detection, ultimately leading to worse colon cancer prognosis in obese patients.

In conclusion, in colorectal cancer groups treated with surgical intervention, hemodilution from increased plasma volume may be responsible for the decreased serum CEA concentration seen in patients with higher BMI. Obesity might be one of the factors that affect CEA value, leading to loss of sensitivity and diagnostic accuracy in the CEA test. This association needs to be confirmed by additional prospective studies that include postoperative surveillance data or larger proportions of high-BMI patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965;121:439–62.
2. Fletcher RH. Carcinoembryonic antigen. Ann Intern Med 1986;104:66–73.
3. Oettgen HF, Schwartz MK, Stearns M, et al. Preoperative carcinoembryonic antigen level as a prognostic indicator in colorectal cancer. N Engl J Med 1978;299:448–51.
4. Kieninger G, Fischer R, Hornung A, Stumpf E, Anderer FA, Staab HJ. Eighty-four potential second-look operations based on sequential carcinoembryonic antigen determinations and clinical investigations in patients with recurrent gastrointestinal cancer. Am J Surg 1985; 149:198–204.
5. Gimnez N, Jo J, Filella X, Molina R, Ballesta AM. Carcinoembryonic antigen in staging and follow-up of patients with solid tumors. Tumor Biol 1995;16:32–41.
6. Mackay IR, Stevens DP. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet 1973;2:1238–9.
7. Chretien PB, Silverman NA, Alexander JC. Effect of age and cigarette smoking on carcinoembryonic antigen levels. JAMA 1976;235:1975–9.
8. Austin GE, Bhatnagar M, Tewari HB, Bhatnagar J. Comparison of carcinoembryonic antigen in tissue and serum with grade and stage of colon cancer. Anticancer Res 1999;19:2181–7.
9. Wahren B, Rieger A. CEA levels at recurrence and metastases. Scand J Gastroenterol 1975;10:869–74.
10. Begent RH. The value of carcinoembryonic antigen measurement in clinical practice. Ann Clin Biochem 1984;21:231–8.
11. Myung SC, Kim YS, Kim T, Han JH, Ahn SH, Chang IH. The clinical significance in healthy men of the association between obesity related plasma hemodilution and tumor marker concentration. J Urol 2009;181:567–72.
12. Freedland SJ, Moul JW, Amling CL, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007;298:2275–80.
13. Humphrey PA, Vollmer RT. Tumor volume in prostate cancer and serum prostate-specific antigen. Analysis from a kinetic viewpoint. Am J Clin Pathol 2003;119:80–9.
14. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
15. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989; 5:303–11, discussion 12–3.
16. Boer P. Estimated lean body mass as an index for normalization of body fluid volumes in humans. Am J Physiol 1984;247:F632–6.
17. Gunter MJ, Leitzmann MF. Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes. J Nutr Biochem 2006;17: 145–56.
18. Huang XF, Chen J. Adiponectin and signal pathways in obesity-induced colon cancer. Gut 2009;58:1169, author reply -70.
19. Vollmer RT, Humphrey PA. Tumor volume in prostate cancer and serum prostate-specific antigen. Analysis from a kinetic viewpoint. Am J Clin Pathol 2003;119:80–9.
20. Messerli FH, Sundgaard-Riise K, Reisin E, Dreslinski G, Dunn FG, Frohlich E. Disparate cardiovascular effects of obesity and arterial hypertension. Am J Med 1983;74:808–12.
21. Banez LL, Hamilton RJ, Partin AW, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007;298:2275–80.
22. Lye WC, Tambyah P, Leong SO, Lee EJ. Serum tumor markers in patients on dialysis and kidney transplantation. Adv Perit Dial 1994;10:109–11.
23. Wolff JM, Ting O, Borchers H, Rohde D, Jakse G. Serum levels of prostate specific antigen in men on hemodialysis. Anticancer Res 2000;20:5191–3.
24. Tan E, Gouvas N, Nicholls RJ, Ziprin P, Xynos E, Tekkis PP. Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. Surg Oncol 2009;18:15.
25. Korner H, Soreide K, Stokkeland PJ, Soreide JA. Diagnostic accuracy of serum-carcinoembryonic antigen in recurrent colorectal cancer: a receiver operating characteristic curve analysis. Ann Surg Oncol 2007;14:417–23.
26. Wanebo HJ, Rao B, Pinsky CM, et al. Preoperative carcinoembryonic antigen level as a prognostic indicator in colorectal cancer. N Engl J Med 1978;299:448–51.
27. Takagawa R, Fujii S, Ohta M, et al. Preoperative serum carcinoembryonic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. Ann Surg Oncol 2008;15: 3433–9.
28. Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem 2001;47:624–30.
29. Park IJ, Choi GS, Lim KH, Kang BM, Jun SH. Serum carcinoembryonic antigen monitoring after curative resection for colorectal cancer: clinical significance of the preoperative level. Ann Surg Oncol 2009; 16:3087–93.
30. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295:1549–55.
31. Rundle A, Neugut AI. Obesity and screening PSA levels among men undergoing an annual physical exam. Prostate 2008;68:373–80.
32. Ohwaki K, Endo F, Muraishi O, Hiramatsu S, Yano E. Relationship between prostate-specific antigen and hematocrit: does hemodilution lead to lower PSA concentrations in men with a higher body mass index? Urology 2010;75:648–52.