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Influence of Smoking Status and Body Mass Index on Serum Carcinoembryonic Antigen Concentration in Patients with Thoracic Diseases

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Abstract

BACKGROUND: Although the serum carcinoembryonic antigen (CEA) concentration is the well-known prognostic marker of non-small cell lung cancer (NSCLC), serum CEA concentration has been reported to be affected by smoking status and body mass index (BMI). There are no previous investigations that examined the relationship between BMI and serum CEA concentration in thoracic disease, including NSCLC. METHODS: Consecutive 384 NSCLC patients and 87 patients with benign thoracic disease were enrolled. The relationship between serum CEA concentration and smoking status and BMI in patients with benign thoracic benign disease and NSCLC was examined. RESULTS: In patients with benign thoracic disease, serum CEA concentration significantly increased with smoking status and Brinkman index. However, serum CEA concentration was not related with BMI. Serum CEA concentration of patients with NSCLC was significantly higher than those with benign disease. In NSCLC patients, the relationship between serum CEA concentration and smoking status was also found. A significant relationship between serum CEA concentration and smoking status was also found in patients with adenocarcinoma which is known to have weaker associations with smoking in carcinogenesis. On the other hand, we failed to find the relationship between serum CEA concentration and BMI in NSCLC patients. CONCLUSION: Serum CEA concentration may be affected by smoking status but not BMI in our Japanese patients with thoracic disease.

Keywords

CEA, Smoking Status, Body Mass Index, Benign Thoracic Disease, Non-Small Cell Lung Cancer

1. Introduction

Carcinoembryonic antigen (CEA) is one of these serologic markers of malignant tumors, including non-small cell lung cancer (NSCLC). Previous investigations showed the prognostic significance of serum CEA concentration in NSCLC [1] [2] [3].

However, some variables affect the serum CEA concentration. Cigarette smoking is one of the well-known variables associated with increased CEA concentrations. Previous investigations showed that serum CEA level were significantly higher in cigarette smokers than in non-smokers [4] [5].

Furthermore, other previous investigations had also shown that higher body mass index (BMI) is associated with lower CEA concentration in colorectal cancer patients [6] [7] and healthy males [8] [9].

In patients with thoracic disease, Okada *et al.* [10] reported the effect of smoking status on serum CEA concentration in NSCLC. However, to our knowledge, there are no previous investigations that showed the effect of BMI on serum CEA concentration in patients with NSCLC. As the effect of BMI on serum CEA concentration in patients with thoracic diseases is uncertain, we hypothesized that the prognostic precision of the serum CEA concentration in NSCLC might be affected by smoking and BMI status. Therefore, we designed the present study that examined the relationship between serum CEA concentration in thoracic begin disease and NSCLC.

2. Patients and Methods

This retrospective study had institutional review board approval, and the need to obtain patient consent was waived. Consecutive NSCLC patients who examined preoperative serum CEA concentration and underwent surgery from 2008 to 2013 in our hospital were enrolled into the present retrospective study. Furthermore, patients with benign thoracic disease who also underwent surgery during same period were also enrolled. Among these patients with benign diseases, patients who were not examined preoperative serum CEA concentration and those with clinical history of malignant disease were excluded. The collected records of 384 consecutive NSCLC patients and 87 patients with benign thoracic disease were reviewed retrospectively. The lifetime consumption of cigarette smoke was assessed using the Brinkman index (BI), calculated by the numbers of cigarettes smoked per day multiplied by the smoking years [11]. Based on the BI, patients were subdivided into 3 groups: never smoker (BI = 0), light to moderate smoker (BI = 1 - 500) and heavy smoker (BI > 500). The preoperative BMI was calculated as weight in kilograms divided by height in meters squared. According to the previous investigation [6], the following categories were used: lower range of normal weight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5 - 24.0 kg/m^2) and overweight (BMI > 24.0 kg/m^2). The clinicopathologcal factors of patients were shown in **Table 1** and **Table 2**.

We used Wilcoxon rank-sum tests to assess associations between serum CEA concentration and smoking status, Brinkman index and BMI, with p-values

computed using the normal approximation. All statistical analyses were performed using JMP (SAS Institute Inc., Cary, NC, USA).

3. Results

The study included 87 patients with benign thoracic disease, including 6 benign lung tumors, 33 benign mediastinal tumors, 37 inflammatory lung diseases and 11 others (Table 1). In NSCLC patients, there were 296 adenocarcinomas and 88 other histologic types (Table 2).

The serum CEA concentration (mean ± S.D.) in patients with benign disease was 2.82 ± 52.67 ng/ml, while patients with NSCLC was 97.38 ± 27.60 ng/ml ($p < 0.001$).

In patients with benign thoracic diseases, the serum CEA concentration (mean ± S.D.) of patients with never smoker and current/former smoker were 2.720 ± 3.287 and 2.957 ± 1.519 ng/ml, respectively ($p = 0.016$). Similarly, the serum CEA concentration (mean ± S.D.) of BI = 0, BI = 1 - 500 and BI > 500 group were 2.720 ± 3.287, 2.361 ± 1.014l and 3.521 ± 1.719 ng/ml, respectively. Although, we failed to find a statistical difference between BI = 0 and BI = 1 - 500 groups ($p = 0.408$), the serum CEA concentration of BI > 500 group was significantly higher (BI = 0 vs. BI > 500: $p = 0.003$, BI = 1 - 500 vs. BI > 500: $p = 0.018$). On the other hand, the serum CEA concentration (mean ± S.D.) of BMI < 18.5, BMI = 18.5 - 24.0 and BMI > 24.0 groups were 2.229 ± 1.370, 2.651 ± 1.736 and 3.307 ± 4.092 ng/ml, respectively (BMI > 24 vs. 18.5 - 24: $p = 0.558$,

Table 1. Clinical characteristics of patients with benign thoracic disease.

		No. of patients
Age	≤65	48
	>65	39
Gender	Male	47
	Female	40
Smoking status	Never	50
	Current/former	37
Brinkman index	0	50
	1 - 500	18
	>500	19
Histology	Benign lung tumor	6
	Benign mediastinal tumor	33
	Inflammatory lung disease	37
	Others	11
CEA	Normal	78
	High	9
BMI	<18.5	7
	18.5 - 24	53
	>24	27

CEA: carcinoembryonic antigen, BMI: body mass index.

Table 2. Clinical characteristics of patents with non-small cell lung cancer.

		No. of patients
Age	≤65	125
	>65	259
Gender	Male	198
	Female	186
Smoking status	Never	172
	Current/Former	212
Brinkman index	0	172
	1 - 500	58
	>500	154
Histology	Adenocarcinoma	296
	Others	88
pStage	I	296
	II-IV	88
pT status	pT1	259
	pT2-3	125
pN status	pN0	326
	pN1-2	58
CEA	Normal	282
	High	102
BMI	<18.5	59
	18.5 - 24	219
	>24	106

CEA: carcinoembryonic antigen, BMI: body mass index.

BMI > 24 vs. <18.5: p = 0.406, BMI = 18.5 - 24 vs. <18.5: p = 0.519). There are no significant differences of serum CEA concentration among BMI groups. Using box and whisker plot, we further determined the distribution of serum CEA concentration in each subgroup (Figure 1).

In patients with NSCLC, the serum CEA concentration (mean ± S.D.) of patients with never smoker and current/former smoker were 5.085 ± 13.320 and 9.234 ± 35.093 ng/ml, respectively ($p < 0.001$). Similarly, serum CEA concentration (mean ± S.D.) of BI groups were BI = 0: 5.086 ± 13.320, BI = 1 - 500: 7.071 ± 15.002 and BI > 500: 10.049 ± 40.150 ng/ml, respectively (BI > 500 vs. 0: $p < 0.001$, BI > 500 vs. 1 - 500: p = 0.0456 and BI = 1 - 500 vs. 0: p = 0.187). There was also a trend towards an association between serum CEA concentration and BI but the difference between BI = 0 and BI = 1 - 500 group did not reach statistical significance. The serum CEA concentration (mean ± S.D.) of BMI < 18.5, BMI = 18.5 - 24.0 and BMI > 24.0 groups were 6.314 ± 62.886, 5.842 ± 12.110 and 5.572 ± 15.402 ng/ml, respectively (BMI > 24 vs. 18.5 - 24: p = 0.313, BMI > 24 vs. <18.5: p = 0.058, BMI = 18.5 - 24 vs. <18.5: p = 0.172). We also failed to find the significant differences of serum CEA concentration among BMI groups in patients with NSCLC. Box and whisker plots summarise these distributions (Figure 2).

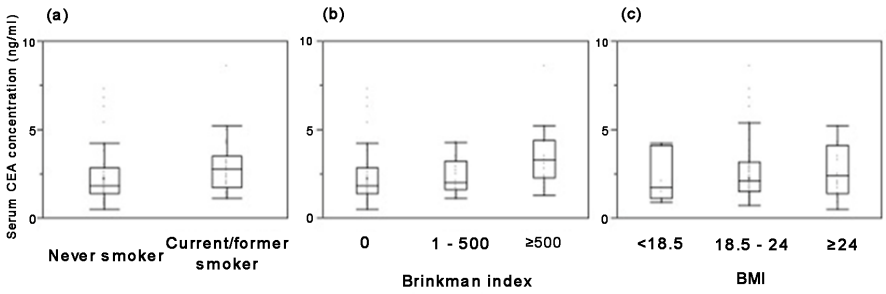

Figure 1. Box and whisker plot of patients with benign thoracic disease stratified by smoking status (a), BI (b) and BMI (c) demonstrating a difference in serum CEA concentration. BI: Brinkman index, BMI: body mass index, CEA: carcinoembryonic antigen.

In patients with adenocarcinoma, smoking is generally believed to play a less vital role in the cause or growth of the tumor compared with other types. Therefore, we also examined the relationship between serum CEA concentration and smoking status in patients with adenocarcinoma. The results of serum CEA concentration (mean ± S.D.) in patients with adenocarcinoma were as follows: never smoker (5.244 ± 13.710 ng/ml) vs. current/former smoker (9.417 ± 41.910 ng/ml): $p = 0.005$; BI = 0 (5.244 ± 13.710 ng/ml) vs. BI > 500 (11.752 ± 51.496 ng/ml): $p < 0.001$, BI > 500 vs. BI = 1 - 500 (5.096 ± 9.549 ng/ml): $p = 0.013$ and BI = 1 - 500 vs. BI = 0: $p = 0.784$.

4. Discussion

The present study is the first investigation that examined the relationship between BMI and serum CEA concentration in thoracic disease, including NSCLC. Our results showed a clear relationship between smoking status and serum CEA concentration in both benign thoracic diseases and NSCLC. To our knowledge, there are no previous investigations that denied an association between smoking and serum CEA concentration. Smoking is a major risk factor for lung cancer, especially in patients with squamous cell carcinoma. In patients with adenocarcinoma, smoking is generally believed to play a less vital role in the cause or growth of the tumor compared with other types. We also showed a clear relationship between smoking status and serum CEA concentration in patients with adenocarcinoma. Okada *et al.* [10] reported the effect of smoking status on interpretation of serum CEA concentration. They concluded that smoking status of patients should be taken into account when serum CEA concentrations are checked in NSCLC [10]. We should consider the possibility of loss of sensitivity and accuracy in the CEA test by smoking status.

BMI had been also reported to be one of the factors that affect serum CEA concentration, and serum CEA concentration significantly decreased with increasing BMI [6] [7] [8] [9]. Thus Park *et al.* [6] also concluded that the BMI status of patients should be taken into account during assessment of serum CEA during the surveillance of colorectal cancer. The reason for the relationship between BMI and serum CEA concentration has been considered to be the hemodilution effect of obesity patients [6] [7] [8] [9]. In other words, the larger

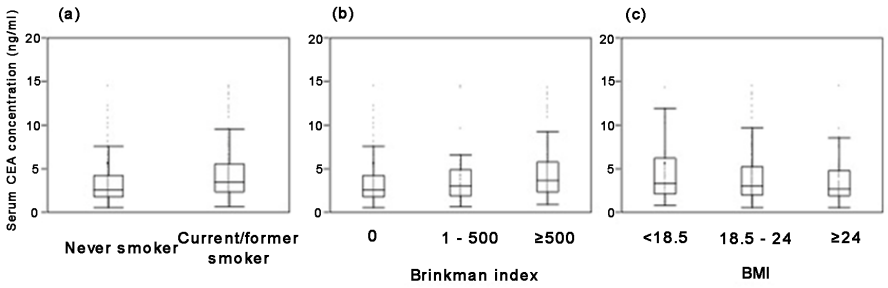

Figure 2. Box and whisker plot of patients with NSCLC stratified by smoking status (a), BI (b) and BMI (c) demonstrating a difference in serum CEA concentration. BI: Brinkman index, BMI: body mass index, CEA: carcinoembryonic antigen, NSCLC: non-small cell lung cancer.

vascular volume of obese patients might cause a dilution effect of CEA [8]. Furthermore, Li *et al.* [9] hypothesize other two possible reasons: First, an inflammatory state caused by obesity may result in greater leakage of CEA into the serum. Second, insulin resistance of obesity patients might contribute to the increased CEA. However, we failed to find this relationship in both benign thoracic diseases and NSCLC. The biological mechanism underlying this observation is not entirely clear although our findings are consistent with other previous investigations [12] [13]. One of possible reasons for this discrepancy is small number of extremely obese patients. The patients with BMI > 27.5 is only 4.7% (22/471) of our study population. On the other hand, the ratio of patients with BMI > 27.5 in previous study population of Park *et al.* [7], Chang *et al.* [8] and Li *et al.* [9] were 6.9% (224/3259), 8.6% (752/8776) and 14.6% (341/2359), respectively. Furthermore, our study population is Japanese patients. There are no previous investigations from Japan that showed the relationship between BMI and serum CEA concentration. Yoshiike *et al.* [14] reported that the standardized prevalence of obesity (BMI > or = 30.0) in Japanese adults was quite low compared with the data in western populations. Taken together, because of small number of obese patients, there is a possibility that we might fail to find a dilution effect of CEA.

Conversely, other previous investigations [12] [13] reported that no association was found between serum CEA concentration and BMI in healthy cohorts. Our findings are consistent with these results [12] [13]. In addition to cigarette smoking, serum CEA concentration might be affected by several factors, including age, hypothyroidism and white blood cell count [9]. The reason for these conflicting findings [6] [7] [8] [9] [12] [13] might be explained by these factors. Further studies are warranted.

Our study's main limitations relate that all patients were surgery patients and the number of patients was small. Therefore, a large cohort study will be required to confirm our results.

5. Conclusion

In conclusion, serum CEA concentration may be affected by smoking status, but

we failed to find a relationship between BMI and serum CEA concentration in both benign thoracic diseases and NSCLC.

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