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Increase of Carcinoembryonic Antigen Level in Serum Is Associated with Metabolic Factors and Lifestyle

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***Abstract*—Carcinoembryonic antigen (CEA) has been a critical indicator for diagnosis of some cancers, however, CEA levels might increase in certain physiological conditions. We investigate the relationship between CEA levels and nonmalignant conditions based on physical examination and laboratory data of serum from 1601 individuals attending Jinan Central Hospital. Our results showed that CEA level increased significantly with agein both genders. Subjects were classified into different groups according to metabolic factors including BMI, fasting glucose, serum lipids and blood pressure, and lifestyle including cigarette smoking and alcohol consumption. In women, CEA levels are higher in those with higher BMI, hyperlipidemia and hypertension than in normal group, whereas in men, CEA level in those with fasting hyperglucoseis significantly higher than those with normal glucose. In male smokers and drinkers, CEA levels tend to go up along with the increase of cigarette and alcohol consumption. After adjustment of age, CEA level is positively correlated with the fasting glucose, smoking and alcohol consumption in men, while with BMI in women. These results indicate that CEA levels can change dramatically under nonmalignant circumstances including age, BMI, fasting glucose, serum lipids, blood pressure, cigarette smoking, and alcohol consumption factors. This finding suggests that CEA elevation in non-malignant conditions should be taken into account while making diagnosis of cancers.**

Index Terms— **Carcinoembryonic antigen (CEA); Body mass index (BMI); Metabolic factors; Lifestyle.**

I. INTRODUCTION

Carcinoembryonic antigen(CEA) is an oncofetal glycoprotein with a molecular weight of 180 to 200kDa[1]. CEA is over expressed in adeno carcinomas in the colon and other organs including pancreas, lung, prostate, urinary bladder, ovary and breast, so it is widely used as a tumor marker[2-6]. It can also be elevated in some non-malignant conditions, such as cirrhosis, ulcerative colitis, chronic renal failure, hypothyroidism, pancreatitis and even cigarette smoking, and some chronic inflammatory diseases. CEA elevation in such non-malignant conditions is usually less than 10ng/ml[7-10]. Therefore, it would be important to distinguish such elevations of CEA levels in non-malignant diseases with malignancies when using this biomarker for diagnosis. In the current study, we investigated the CEA levels in serum from individuals who underwent regular health checkup, and association with non-malignant conditions including age, body mass index (BMI), fasting glucose, serum lipids, blood pressure, cigarette smoking and alcohol consumption. The aim of this study was to evaluate whether CEA levels were associated with multiple factors in non-malignant conditions in Jinan city.

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II. MATERIALS AND METHODS

Clinical characteristics of study subjects-People of physical examination

Between September, 2012 and November2012, there were 1,601 people (1,219 men and 382 women) from physical examination in Jinan Central Hospital. All those with tumor, pregnancy, severe liver and kidney dysfunction, or autoimmune diseases were excluded in this study. All individuals agreed to participate in the study and signed the consent forms. The study protocol was approved by the Ethics Committee of our Hospital. Clinical characteristics of study subjects are included in Table 1.

A. Blood sample collection

Serum samples were obtained on a fasting state for at least 8hours, and peripheral blood samples were collected in 2-3ml without containing anticoagulant, and stayed on ice for 15 min, and then centrifuged at 3,500rpm for 10minto separate serum.

B. Carcinoembryonic Antigen(CEA) Determined by Micro Particle Enzyme Immunoassay

The CEA assay was performed by the TOSOH CORPORATION kit (D810672, Japan) and automatic chemiluminescence detector (AIA-2000 ST, TOSOH CORPORATION, Japan), which is based on micro particle enzyme immunoassay technology. The results were expressed in nano grams per milliliter (ng/ml). The assay was performed according to the manufacturer's instructions.

C. Fasting Glucose and Serum Lipid Assay

The fasting glucose (GLU) and triglyceride (TG), total

cholesterol (TC), high density lipoprotein(HDL) and low density lipoprotein(LDL) levels in serum were measured by using the Roche cobase411 chemistry system(Japan). The results were expressed in millimole per liter (mmol/L). The assay was performed according to the manufacturer's instructions.

D. Statistical Analysis

Statistical analysis was conducted with SPSS software (Version 20.0; SPSS Inc., Chicago, USA). Values of CEA are presented as the mean ±standard deviation. The Student t-test was used to analyze differences between two groups, one-way ANOVA was used to compare multiple groups. $P < 0.05$ was considered to indicate a statistically significant difference.

III. RESULTS

A. The CEA Levels In the Population of Physical Examination People

The CEA level detected in the blood samples from the 1601 physical examination people was in the range of 0.10-61.20ng/ml. The median CEA level was 3.20ng/ml, with the average being 3.86ng/ml. The CEA level detected in the blood samplesfrom the 1219 men was in the range of 0.40-61.20ng/ml with the median CEA level was 3.50ng/ml and the average being 4.16ng/ml. The CEA level detected in the blood samples from the 382 women was in the range of 0.10-13.60ng/ml with the median CEA level was 2.40ng/ml and the average being 2.89ng/ml. The mean CEA level was significantly higher in men (4.16±0.11ng/ml) than that in women (2.89±0.89ng/ml) (P< 0.01), as shown in Table 1.

Table 1: Clinical Characteristics of Study Subjects

Variables	Groups	# of Men	# of Women
Age（y）	<40	103	44
	40-60	488	155
	=60	628	183
Body Mass Index (BMI)	lower	23	18
	normal	435	214
	overweight	588	116
	obesity	173	34
Fasting glucose	Hyperglucose normal	153	23
		1066	359
Serum Lipids	Hyperlipidemia normal	468	105
		751	277
Blood pressure	hypertension normal	611	133
		608	249
Cigarette smoking（y）	Nonsmoking	920	n/a*
	<10	44	n/a
	10-20	77	n/a
	20-30	90	n/a
	=30	85	n/a
Alcohol consumption（y）	<10	1047	n/a
	10-20	36	n/a
	20-30	69	n/a
	=30	67	n/a

*n/a = not available

B. Age

Physical examination people were divided into three groups according to the age. As showed in Figure 1, the CEA level increased with age. The CEA levels of the <40, 40-60, ≥60 groups were 2.68±0.26ng/ml, 3.87±0.59ng/ml, 4.62±0.80ng/ml, respectively in men, the CEA values of 40-60, ≥60 groups were significantly higher than the CEA value of <40 group (P<0.05, P<0.01 respectively), moreover, the CEA values of ≥60 group was significantly higher than the CEA value of 40-60 group (P<0.05). The CEA levels of the <40, 40-60, ≥60 groups were 1.88±0.86ng/ml, 2.23±1.09ng/ml, 3.68±0.26ng/ml, respectively in women, there was no significant difference between the <40 group and 40-60 group, however, the CEA value of ≥60 group was significantly higher than the other 2 groups(P<0.05).

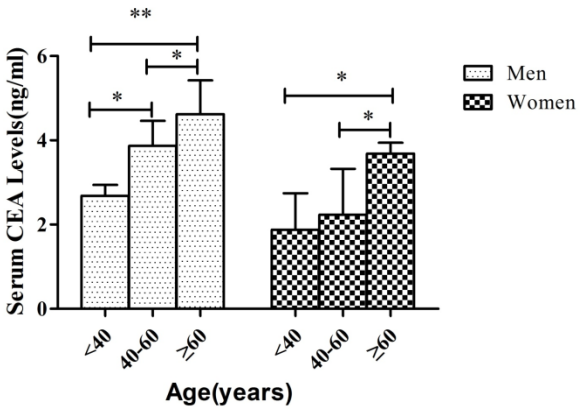

Fig 1:The CEA level increased with age. Data of CEA levels in serum associated with age in men and women were presented as mean±SD. *P< 0.05, **P< 0.01.

C. Body Mass Index (BMI)

BMI was calculated as weight in kilograms divided by height in meters squared. Physical examination people were divided into four groups according to the Chinese prevalence of overweight and obesity among adults. The ranges of body weight were divided into 4 groups: lower than normal weight (BMI<18.5kg/m2), normal weight (BMI=18.5-24.0kg/m2), overweight (BMI=24.0-27.9kg/m2) and obesity (BMI>28.0kg/m2). As showed in Figure 2, there were no significant differences among the men subgroups. In women the CEA values of overweight and obesity groups were significantly higher than that of normal weight group, P<0.05 and P<0.01, respectively.

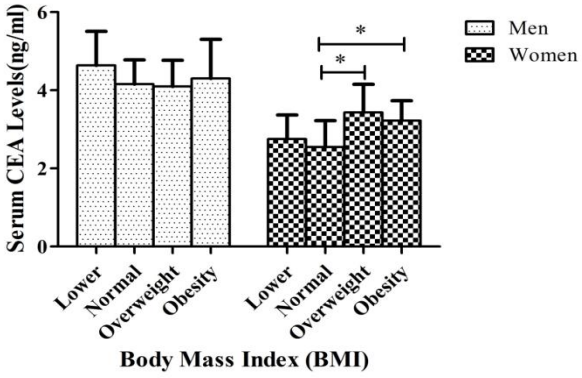

Fig 2: The CEA values of overweight and obesity groups were found significantly higher than that of normal weight group in females. There were no significant differences in males. Serum CEA levels and BMI in men and women were presented as mean±SD. *P< 0.05.

D. Fasting Glucose

According to the American Diabetes Association(ADA) recommended diagnostic criteria for diabetes(fasting glucose >7.0mmol/L), physical examination people were divided into hyperglucose and normal groups in men and women respectively. As showed in Figure 3, the CEA values of hyperglucose group(4.93±0.93ng/ml) were significantly higher than that of normal group in men(4.05±0.10ng/ml), P<0.05. There were no significant different between hyperglucose group and normal group in women.

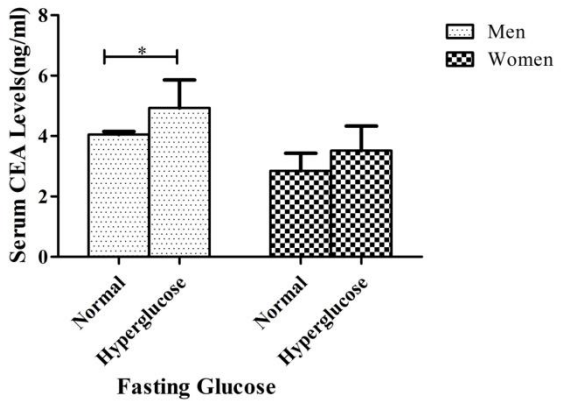

Fig 3: CEA values of hyperglucose group were significantly higher than that of normal group in males. There were no significant different between hyperglucose group and normal group in women. Serum CEA levels associated with fasting glucose in men and women were presented as mean±SD. *P< 0.05.

E. Serum Lipids

According to the Chinese prevalence of dyslipidemia among adults, the hypercholesterolemia (TCH>6.22mmol/L), hypertriglyceridemia (TG>2.26mmol/L), mixed hyperlipidemia (TCH>6.22mmol/L and TG>2.26mmol/L) and low high-density lipoprotein hyperlipidemia (HDL<1.04mmol/L) treated as hyperlipidemia. Physical examination people were divided into hyperlipidemia and normal groups in men and women respectively. As showed in Figure 4, the CEA values of hyperlipidemia group(3.33±0.13ng/ml) were significantly higher than the CEA value of normal group in women, P<0.05. There was no significant difference between hyperlipidemia group and normal group in men.

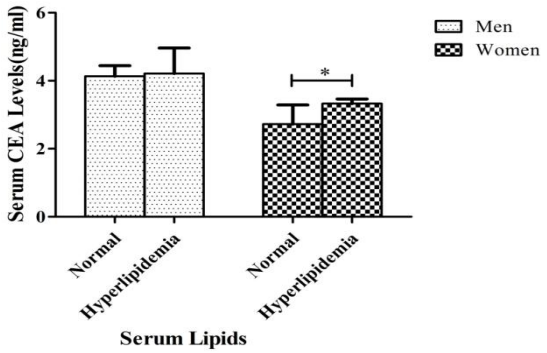

Fig 4: CEA values of hyperlipidemia group were significantly higher than that of normal group in females. There was no significant difference between groups in males. Data of serum CEA levels and serum lipids in men and women were presented as mean±SD. *P< 0.05.

F. Blood Pressure

Blood pressure was measured in the sitting position after a 10 min rest. According to the World Health Organization(WHO) standards, the physical examination people were divided into hypertension and normal groups in men and women respectively. As showed in Figure 5, the CEA values of hypertensiongroup(3.47±0.51ng/ml) were significantly higher than that of normal group(2.57±0.46ng/ml) in women, P<0.05. No significant difference was found between hypertension group(4.25±0.63ng/ml) and normal group(4.06±0.52ng/ml) in men.

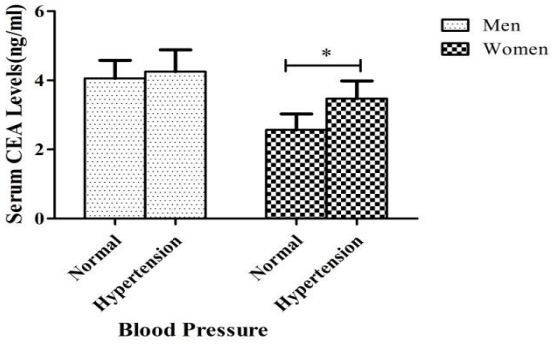

Fig 5: CEA levels of hypertension group were significantly higher than that of normal group in females, but not significantly different in males. CEA levels associated with blood pressure in men and women were presented as mean±SD, *P< 0.05.

G. Cigarette Smoking

All the women without smoking history were excluded. The effect of cigarette smoking on CEA levels was investigated only in 1219 men. The CEA levels in men smokers and nonsmokers were compared based on smoking history, the results were showed in Figure 6A. There were no statistically different among the nonsmoking, <10 years, 10-20 years groups. The CEA level was significantly higher in smokers of 20-30 years group(5.15±0.42ng/ml) than in nonsmokers (3.64±0.45ng/ml) and <10 years groups(3.94±0.68ng/ml), P< 0.05. The CEA level was significantly higher in the smokers of ≥30 years group(5.57±0.62ng/ml) than that in the nonsmokers (3.64±0.45ng/ml), <10 years(3.94±0.68ng/ml) and 10-20 years groups (4.39±0.62ng/ml), P< 0.01, P< 0.01, P< 0.05,respectively. Compared with those nonsmokers, the individuals with smoking history from less than 10 years to 10-20 years, the CEA levels tend to increase but there is no significant difference.

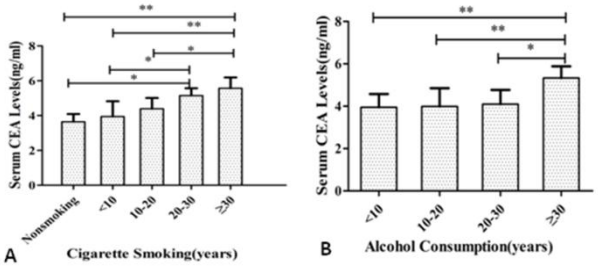

Fig 6: CEA levels in serum are associated with long-term smoking and drinking in males. Consumption of cigarettes (A); and alcohol (B) in men. Data were presented as mean±SD, *P< 0.05, **P< 0.01.

H. *Alcohol Consumption*

Among 382 women, only one person with drinking, therefore, we only investigated the effect on CEA levels of drinking in 1219 men. The results were provided in Figure6B. There was no statistical difference among the <10 years, 10-20 years, 20-30 years groups. The CEA level was significantly higher in drinkers of ≥30 years group(5.33±0.55ng/ml) than in <10 years(3.10±0.63ng/ml), 10-20 years(3.95±0.86ng/ml), 20-30 years(3.99±0.67ng/ml) groups, P< 0.01, P< 0.01, P< 0.05,respectively.

Hyperglycemia, hypertension and hyperlipidemia are common problems among the elderly, and nowadays, it is clear that the smoking and alcohol history are closely related to age. We excluded age as a factor of variation using the covariance analysis, after adjusting age factor, we assessed the correlation between CEA levels and BMI, fasting glucose and serum lipids, blood pressure, smoking and alcohol consumption. For men, there is a significant correlation between CEA levels and fasting glucose levels, smoking and alcohol consumption(P=0.009; P<0.001; P=0.036, respectively); while for women, only BMI seems to affect the CEA level (P=0.042).

IV. DISCUSSION

Although CEA is a useful indicator for monitoring the therapeutic efficacy of surgery in colorectal cancer[2], mildly increased CEA concentrations are associated with several conditions [7, 8]. CEA marker when used in clinical practice needs to be carefully considered. We quantified the effect of seven factors including age, BMI, fasting glucose, serum lipids, blood pressure, drinking and cigarette smoking on serum CEA levels in 1601 subjects who underwent the physical health testing in our hospital. We found positive associations between serum CEA concentration and fasting glucose levels, smoking and alcohol consumption in men, while for women, only BMI seems to affect the CEA level, these associations remained statistically significant even after adjusting for age.

CEA values in non-malignant conditions can be affected by the metabolic factors, including BMI, fasting glucose, serum lipid and blood pressure. BMI was calculated as weight in kilograms divided by height in square meters. It was previously demonstrated that the obese patients had higher plasma volumes, but not CEA mass, this phenomenon is named obesity-related hemodilution, the serum concentrations of soluble tumor markers in obese population are lower than that in non-obese subjects[11-14]. Our study suggests that there were no statistically significant differences among the 4groupsin males (lower range of normal weight, normal weight, overweight and obesity), unlike it was the reported previously that the CEA values of overweight, obesity groups were significantly higher than those of normal weight group in women, although the mechanism of this phenomenon has not been fully explained. The possible mechanism for this phenomenon is that women with a high BMI and low physical activity had higher levels of estrone, estradiol, and free estradiol, and lower levels of sex hormone binding globulin (SHBG) than women with a similar BMI who were active or with low BMI[15]. Women with elevated levels of estrogens have increased risk of developing breast cancer[16]. Our results showed that the higher level of CEA is associated with the increase of BMI only in females. Moreover, obesity is a danger to health, the International Agency for Research on Cancer estimates that 25% of cancer cases worldwide are caused by overweight or obesity and a sedentary lifestyle[14], according to the above reporting body weight and BMI were improved by physical activity, with decreasing the expression of CEA[17-20].

Recently, Lee Ji-Won et alreported that CEA was positively correlated with fasting glucose, TG, TC and LDL[21]. Our study has also revealed a positive association of the CEA value of hyperglucose(elevated fasting glucose in blood), the hyperglucosegroup was significantly higher than that of normal group in males, and this association remained statistically significant difference even after adjusting age. The possible underlying mechanism to explain the observed link between hyperglucose and serum CEA is that insulin has been shown to affect growth of normal and neoplastic epithelial cells, and to have mitogenic actions in vitro and in experimental models, either directly or indirectly through insulin-like growth factor-1 (IGF-1)[22]. IGF-1 enhances division of normal cells and inhibits cell death, which is also related to tumor proliferation. It has been demonstrated that high circulating levels of IGF-1 was associated with increased risk of some cancers, such as breast, colon, and prostate[23]. A study reported that an antisense IGF-I gene that blocks the corresponding IGF sequences may be the reason for the decrease of CEA [24]. Thus, insulin resistance may be associated with the increase of CEA. This may explain the finding of an association between hyperglucose and serum CEA in males. In females the CEA tended to increase in the hyperglucose group but did not reach significant difference with the normal group. Further studies are needed to explore the underlying mechanism between hyperglucose and serum CEA.

Serum CEA levels may also be affected by lifestyle such as cigarette smoking and alcohol consumption. The present study has revealed a positive association of former/current smoking status with serum CEA levels, compared with never smoking. This finding is supported by previous observations that serum CEA levels were significantly higher in smokers and that cigarette smoking is associated with increased serum CEA levels regardless of age or the number of cigarettes consumed. The results also show that after cessation of smoking, CEA levels decline to levels similar to those of nonsmokers within a three-month period[7, 25-27].The elevated serum CEA levels were sometimes found in nonmalignant diseases, especially in chronic lung disease. Furthermore, its elevation was found even in ulcerative colitis or liver cirrhosis. Fukuda et alreported that Thirty two of CEA-positive heavy smokers revealed normal respiratory functions and chest X-P and did not suffer from ulcerative colitis or liver cirrhosis[7]. Therefore, a positive CEA level of these cases depended only on cigarette smoking.

Few reports have addressed the question of a positive association of alcohol consumption with the elevated serum CEA levels.The present study has revealed the CEA level was significantly higher in drinkers of ≥30 years group than in <10 years, 10-20 years, 20-30 years groups. The possible explanation is that the alcohol consumption caused liver dysfunction leading to elevation of serum CEA concentrations. The biochemical mechanism show alcohol consumption results in elevated serum CEA level still need to be investigated in the future.

There are some limitations with this study. First of all, it is not clear whether the analysis of this restricted people introduced a selection bias, and these findings may or may not reflect the situation in the overall population. Secondly, we analyzed only male smokers and drinkers and therefore this result is difficult to generalize to females. Lastly, serum CEA is known to be elevated in other non-malignant conditions, such as hypothyroidism and advanced stage of lung diseases. We did not include these disorders as confounding variables, because their prevalence is considered to be very low among the study population.

V. CONCLUSION

In conclusion, the present study reports a positive association between the elevation of serum CEA and each parameter such asage, BMI, fasting glucose, serum lipids, blood pressure, cigarette smoking and alcohol consumption. After adjusting age, it has demonstrated that there is a significant correlation between CEA levels and fasting glucose levels, smoking and alcohol consumption in males and a significant correlation between BMI and the CEA level in females. Therefore, metabolic factors and lifestyle can induce significant fluctuation of CEA levels which may mislead to the interpretation of the CEA levels while making diagnosis.

COMPETING INTERESTS

No potential conflicts of interest were disclosed by the authors.

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