Serum carcinoembryonic antigen is associated with arterial stiffness in Korean adults

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Serum carcinoembryonic antigen is associated with arterial stiffness in Korean adults

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<ABSTRACT>

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Background: Carcinoembryonic antigen (CEA), widely used tumor markers, has been reported to be related with atherosclerosis and cardiovascular disease. However, little is known about relationship between arterial stiffness and CEA. We assessed whether serum CEA level is related with arterial stiffness by measuring brachial–ankle pulse wave velocity (ba-PWV).

Method: A total of 2909 subjects (1767 men and 1142 women) were divided into quartiles according to CEA level: Q1 (CEA < 1.3 mg/dl), Q2 (1.3 mg/dl ≤ CEA < 1.9 mg/dl), Q3 (1.9 mg/dl ≤ CEA < 2.7 mg/dl), and Q4 (2.7 mg/dl ≤ CEA) in men; Q1 (CEA < 1.0 mg/dl), Q2 (1.0 mg/dl ≤ CEA < 1.4 mg/dl), Q3 (1.4 mg/dl ≤ CEA < 2.0 mg/dl), and Q4 (2.0 mg/dl ≤ CEA) in women.

Results: The mean values of ba-PWV increased gradually by CEA quartile. After adjusting for significantly correlated variables the ba-PWV was independently associated with CEA ($P< 0.001$). The odds ratios (95% CI) for high ba-PWVs (> 75th percentile; men: 1518 cm/s, women: 1487 cm/s) according to CEA quartile in men were 1.00 (Q1), 1.044(0.659-1.652, Q2), 1.075(0.688-1.681, Q3), and 1.595(1.009-2.520, Q4) after adjusting for age, BMI, blood pressure, resting heart rate, fasting glucose, log(Hs-CRP), LDL-cholesterol, white blood cell count, alcohol intake, smoking and exercise ($P< 0.001$). The odds ratios (95% CIs) in women were 1.00 (Q1), 1.719(0.971-3.032, Q2), 1.793(1.019-3.156, Q3), and 2.330(1.312-4.139, Q4) ($P< 0.001$) after adjusting for age, BMI, blood pressure, resting heart rate, fasting glucose, log(Hs-CRP), total cholesterol, LDL-cholesterol, HDL-cholesterol, uric acid, white blood cell count, alcohol intake, smoking and exercise.

Conclusion: The CEA level might be associated with arterial stiffness which measured by ba-PWV in Korean adults.

Key words: carcinoembryonic antigen; arterial stiffness; brachial–ankle pulse wave velocity

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I. INTRODUCTION

Carcinoembryonic antigen (CEA) is one of the most widely used tumor markers worldwide[1]. It is over expressed in adenocarcinomas in the colon and other organs including the pancreas, stomach, lung, prostate, urinary bladder, ovary, and breast. However, several nonmalignant conditions, including acute and chronic inflammation and other inflammatory-related conditions such as aging and smoking are characterized by increased CEA concentrations[2]. Moreover, increased serum CEA concentrations at the high end of normal were associated with carotid atherosclerosis in Japanese men[3]. Recently, study about elevated serum CEA and metabolic syndrome in female Korean non-smokers was reported[4]. Although the function of CEA has not been fully known, several previous studies have revealed that CEA is involved in atherosclerotic process in which monocytes and macrophages are stimulated to release pro-inflammatory cytokines[5] and eventually induce adhesion molecules on vascular endothelial cells[6]. This may lead to atherosclerosis, cardiovascular disease or metastasis of malignant cells[7-8].

Pulse wave velocity (PWV) is a simple, reproducible and noninvasive measurement that may be a valuable index of both arterial stiffness and atherosclerosis in large populations[9]. PWV has not only been reported to be a marker of vascular damage but also a significant predictor of cardiovascular events and mortality[10-12]. Also, the validity, reliability and reproducibility of this measurement have been confirmed suggesting that brachial- arterial PWV (ba-PWV) could be a useful tool for screening arterial stiffness in primary care settings[13]. Although slight elevation of serum CEA can be observed in apparently healthy individuals, little information is available on the possible association between serum CEA and arterial stiffness in general population. The present study was grounded in the hypothesis that CEA levels may affect arterial stiffness, represented as ba-PWV. The aim of the present study was to evaluate, whether serum CEA level is related with ba-PWV in Korean men and women.

II. MATERIALS AND METHODS

1. Study sample

The study sample consisted of Korean men and women who visited Gangnam Severance Hospital Health Promotion Center for a routine health check-up from May 2007 and August 2010. Among these participants, subjects with any missing covariate information were excluded. Patients with history of anti-diabetic, anti-hypertensive, or lipid-lowering medications, malignancy, stroke, or cardiovascular disease such as coronary heart disease, peripheral artery disease, arrhythmia, congestive heart failure, or valvular heart disease and pregnant women were excluded. Total 2909 subjects (1767 men and 1142 women) were enrolled. Subjects were divided into quartiles by SPSS according to CEA level: Q1 (CEA $<$ 1.3 mg/dl), Q2 (1.3 mg/dl $\leq$ CEA $<$ 1.9 mg/dl), Q3 (1.9 mg/dl $\leq$ CEA $<$ 2.7 mg/dl), and Q4 (2.7 mg/dl $\leq$ CEA) in men; Q1 (CEA $<$ 1.0 mg/dl), Q2 (1.0 mg/dl $\leq$ CEA $<$ 1.4 mg/dl), Q3 (1.4 mg/dl $\leq$ CEA $<$ 2.0 mg/dl), and Q4 (2.0 mg/dl $\leq$ CEA) in women. The Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine approved this study and informed consent was obtained from each participant.

2. Measurements

Blood pressure and resting heart rate (RHR) were measured after more than 5 minutes of rest. Anthropometric measurements were used to calculate body mass index (BMI). To reduce inter-observer variation in measurements, one researcher gathered all anthropometric parameters throughout the study. A questionnaire was used to obtain information about a participant's medical history and lifestyle, including exercise, smoking habits, and alcohol consumption. Those who affirmatively answered the question "Do you currently smoke?" were defined as current smokers, whereas those who answered in the negative were defined as former smokers. In this study, smokers were defined as current smokers. Regular exercise was defined as doing physical activity more than 3 times a week for greater than 30 minutes. Alcohol intake was defined as regular drinks more than one time a week. Subjects were instructed to refrain from alcohol the day before testing as well as smoking, coffee, tea, and pain medication on the day of measurement.

After an overnight fast, serum glucose, total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol levels were measured via enzymatic procedures using an autoanalyzer (Bayer, Terrytown, NY, USA). Low-density lipoprotein (LDL)-cholesterol was calculated by the Friedewald formula [14]. High-sensitivity C-reactive protein (hs-CRP) was measured using a latex-enhanced immunoturbidimetric assay in an ADVIA 1650 Chemistry System (Bayer). CEA were measured via CLIA method using Unicel DXI 800 analyzer (Beckman-Coulter, Chaska, MI, USA). White blood cell count (WBC) was measured using ADVIA 2120i (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Uric acid was measured using a Hitachi 7600-110 Chemistry Autoanalyzer (Hitachi, Tokyo, Japan).

3. PWV measurement

The ba-PWV was measured using a volume plethysmographic instrument (PWV/ABI; Colin Co, Komaki, Japan), which recorded a phonocardiogram, electrocardiogram, volume pulse form, and arterial blood pressure at the left and the right brachial arteries and ankles. The ba-PWV was calculated using time-phase analysis between the right brachial artery pressure and the volume waveforms at both ankles. The distance between the right brachium and the ankle was estimated based on the subject’s height. We used the mean ba-PWV in analyses. Both ba-PWV values were measured after allowing the patient to rest in the supine position for at least 5 minutes in an air-conditioned room (24–26℃).

4. Statistical analyses

All analyses were performed using SPSS for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Mean values of clinical characteristics were shown between men and women. All data were presented as mean value (± standard deviation) and categorical variables were presented as frequencies and percentages. Because of the skewed distribution of hs-CRP and triglyceride, this parameter was logarithmically transformed; however, untransformed raw data are presented for the mean (± standard deviation) in tables.

Pearson's correlation analysis was performed to evaluate the relationships of clinical parameters to ba-PWV. Multiple linear regression analysis with a stepwise forward selection procedure was performed to identify any independent associations between ba-PWV and CEA levels. A high ba-PWV group (> 75th percentile) was defined as greater than 1518 cm/s in men and 1487 cm/s in women. The exact numerical value of ba-PWV is not established yet. It is known to be different according to the age, gender or race. So we put the value of over 75 percentile for the high ba-PWV as previous study did[19, 21]. The odds ratios (95% confidence intervals [CIs]) for high ba-PWV were calculated using a multi-variable logistic regression analysis after adjusting for confounding factors. *P*-values less than 0.05 were considered statistically significant.

III. RESULTS

The clinical and metabolic characteristics of the male (n=1767) and female (n=1142) enrolled in this study are shown in Table 1.

Table 1. Clinical and metabolic characteristics of the study participants

	Male (n=1767)	Female (n=1142)
Age (yrs)	53.1 (9.6)	53.1 (17.4)
BMI (kg/m^2)	24.6 (2.8)	22.5 (2.9)
Systolic blood pressure (mmHg)	126.8 (16.1)	120.3 (18.4)
Diastolic blood pressure (mmHg)	79.1 (9.4)	73.9 (10.7)
Heart rate (beats/min)	73.5 (11.4)	74.9 (11.3)
ba-PWV (cm/s)	1420.4 (228.8)	1378.9 (258.9)
WBC (10^3/μL)	6.27 (1.77)	5.44 (1.56)
Hs-CRP (mg/L)	1.8 (3.6)	1.3 (2.6)
Fasting plasma glucose (mg/dL)	100.4 (21.8)	93.0 (18.1)
Uric acid (mg/dL)	5.9 (1.2)	4.3 (0.9)
Total cholesterol (mg/dL)	191.5 (35.7)	196.5 (34.7)
LDL-cholesterol (mg/dL)	130.3 (36.7)	127.2 (35.2)
HDL-cholesterol (mg/dL)	47.1 (11.2)	56.6 (13.2)
Triglyceride (mg/dL)	135.8 (81.1)	127.2 (35.2)
CEA (ng/mL)	2.1 (1.3)	1.5 (0.9)
Alcohol intake, n (%)	876 (49.6)	544 (47.4)
Current smoker, n (%)	602 (34.1)	91 (7.9)
Former smoker, n (%)	813 (46.0)	82 (7.1)
Nonsmoker, n (%)	352 (19.9)	974 (84.9)
Regular exercise, n (%)	640 (36.2)	529 (46.1)

Numerical data are presented as mean (±standard deviation).
Regular exercise was defined as physical activity ≥3 days/week for greater than 30 minutes.
Alcohol intake was defined as regularly drinks ≥1 day/week.
Note: BMI=body mass index; WBC=white blood cell count; Hs-CRP=high-sensitivity C-reactive protein; HDL=high density lipoprotein; LDL=low density lipoprotein; CEA=carcinoembryonic antigen; ba-PWV=brachial-ankle pulse wave velocity

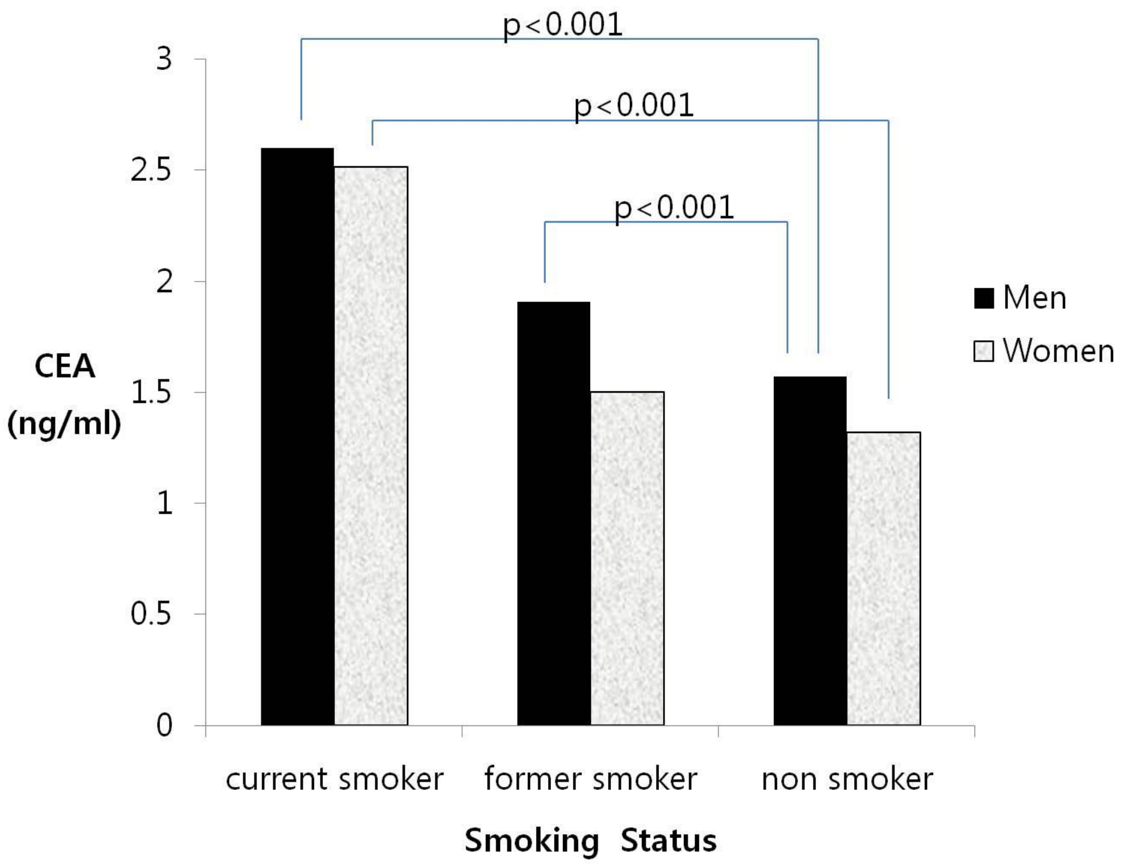

Figure 1. Mean values of CEA according to smoking status

Mean blood pressure, glucose and lipid profile which known as CVD risk factors were all within normal range in male subject except for the mean BMI which was overweight. On Pearson's correlation analysis, ba-PWV in men was correlated with CEA, age, BMI, systolic and diastolic blood pressure, RHR, fasting plasma glucose, log-transformed hs-CRP, LDL-cholesterol, and alcohol intake. In women's correlation analysis, ba-PWV was correlated with CEA, age, BMI, blood pressure, RHR, fasting glucose, WBC count, log-transformed CRP, uric acid, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, alcohol intake and smoking (Table 2).

Table 2. Pearson's correlations between ba-PWV and various parameters

	Pulse Wave Velocity			
	Men		Women	
	r	*p*-value	*r*	*p*-value
CEA (mg/dL)	0.132	<0.001	0.224	<0.001
Age (yrs)	0.514	<0.001	0.309	<0.001
BMI (kg/m^2)	0.088	<0.001	0.187	<0.001
Systolic blood pressure (mmHg)	0.347	<0.001	0.562	<0.001
Diastolic blood pressure (mmHg)	0.294	<0.001	0.537	<0.001
Heart rate (beats/min)	0.164	<0.001	0.172	<0.001
WBC (10^3/μL)	0.041	0.093	0.205	<0.001
Log(hs-CRP) (mg/L)	0.115	<0.001	0.263	<0.001
Fasting plasma glucose (mg/dL)	0.226	<0.001	0.378	<0.001
Uric acid (mg/dL)	0.037	0.120	0.200	<0.001
Total cholesterol (mg/dL)	0.038	0.116	0.184	<0.001
LDL-cholesterol (mg/dL)	0.058	0.016	0.198	<0.001
HDL-cholesterol (mg/dL)	-0.019	0.434	-0.179	<0.001
Log(Triglyceride) (mg/dL)	0.014	0.565	0.244	<0.001
Alcohol intake	-0.119	<0.001	-0.179	<0.001
Current smoking	0.022	0.377	0.074	0.018
Regular exercise	-0.012	0.617	-0.009	0.770

Coefficients (*r*) and *p*-values were calculated using a Pearson's correlation model.

Smoking was defined as current smoking.

Note: BMI=body mass index; WBC=white blood cell count; Hs-CRP=high-sensitivity C-reactive protein; HDL=high density lipoprotein; LDL=low density lipoprotein; CEA=carcinoembryonic antigen; ba-PWV=brachial-ankle pulse wave velocity

After adjusting for significantly correlated variables, ba-PWV was independently associated with CEA in a multiple linear regression analysis with a forward stepwise procedure (*P*< 0.001; Table 3).

Since several variables were correlated with ba-PWV, a forward stepwise multiple regression model would be a better statistical analysis. However, CEA showed strong association with ba-PWV in both Korean men and women.

The odds ratios (95% CIs) for high ba-PWVs (> 75th percentile, men: 1518 cm/s, women: 1487 cm/s) according to CEA quartile in men were 1.00 (Q1), 1.044(0.659-1.652, Q2), 1.075(0.688-1.681, Q3), and 1.595(1.009-2.520, Q4) after adjusting for age, BMI, blood pressure, RHR, fasting glucose, log(Hs-CRP), LDL-cholesterol, white blood cell count, alcohol intake, smoking and exercise (*P*< 0.001; Table 4).

Table 3. Multiple linear regression analysis between pulse wave velocity and clinical variables in Korean men and women

	Men		Women	
	β(95% CI)	*p*-value	β(95% CI)	*p*-value
CEA (mg/dL)	0.055	0.013	0.152	<0.001
Age (yrs)	0.460	<0.001	0.152	<0.001
Systolic blood pressure (mmHg)	0.239	<0.001	0.336	<0.001
Diastolic blood pressure(mmHg)	0.082	0.022	0.172	<0.001
BMI (kg/m^2)	-0.134	<0.001	-0.157	<0.001
Fasting glucose(mg/dL)	0.093	<0.001	0.175	<0.001
Log(Hs-CRP)	0.070	0.002	0.139	<0.001
Heart rate (beats/min)	0.110	<0.001	0.026	0.368
Alcohol intake	-0.019	0.393	0.011	0.685
Smoking	0.014	0.522	-0.047	0.088
Exercise	-0.014	0.537	-0.079	0.985
P-value	<0.001		<0.001	
Adjusted R^2	0.406		0.435	

Note: BMI=body mass index; Hs-CRP=high-sensitivity C-reactive protein

Table 4. Odds ratios (ORs) for high ba-PWV according to serum CEA quartile in Korean adults

	Men			Women		
	CEA(mg/dL)	N(1767)	ORs(95% CIs)	CEA(mg/dL)	N(1142)	ORs(95% CIs)
Q1	<1.3	476	1	<1.0	329	1
Q2	1.3-1.8	446	1.044(0.659-1.652)	1.0-1.3	262	1.719(0.971-3.032)
Q3	1.9-2.6	416	1.075(0.688-1.681)	1.4-1.9	287	1.793(1.019-3.156)
Q4	>2.7	429	1.595(1.009-2.520)	>2.0	264	2.330(1.312-4.139)
	P for trend		<0.001			<0.001

ba-PWV > 75 percentile: men =1518 (cm/s), women=1487 (cm/s)

Men; adjusted for age, blood pressure, BMI, fasting glucose, log(Hs-CRP), heart rate, LDL-cholesterol, white blood cell count, alcohol intake, smoking and exercise

Women; adjusted for age, blood pressure, BMI, fasting glucose, log(Hs-CRP), heart rate, total cholesterol, LDL-cholesterol, HDL-cholesterol, uric acid, white blood cell count, alcohol intake, smoking and exercise

The odds ratios (95% CIs) in women were 1.00 (Q1), 1.719(0.971-3.032, Q2), 1.793(1.019-3.156, Q3), and 2.330(1.312-4.139, Q4) ($P < 0.001$; Table 4) after adjusting for age, blood pressure, BMI, fasting glucose, log(Hs-CRP), heart rate, total cholesterol, LDL-cholesterol, HDL-cholesterol, uric acid, white blood cell count, alcohol intake, smoking and exercise. The mean CEA according to smoking status of men and women were shown in Figure 1. The mean values of ba-PWV according CEA quartiles were shown in Figure 2.

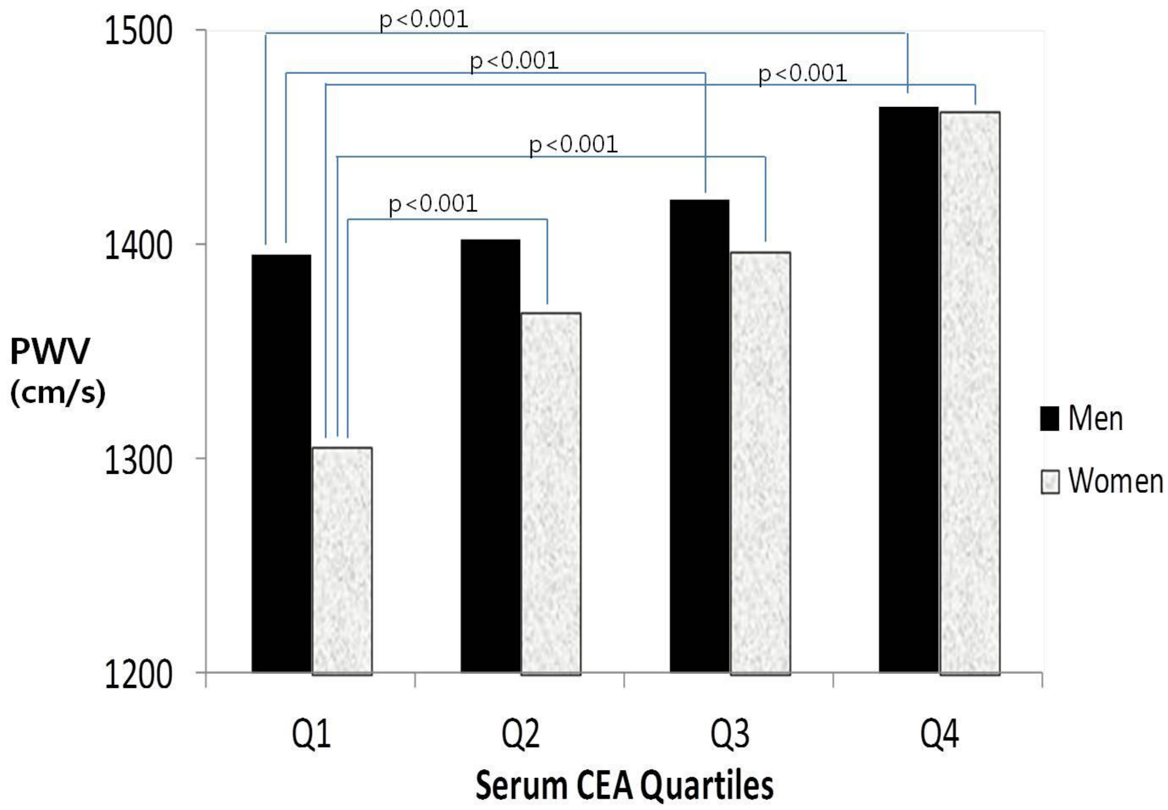

Figure 2. Mean values of brachial-ankle pulse wave velocity according to CEA quartile

IV. DISCUSSION

In the current study, we found that CEA level is associated with arterial stiffness in Korean men and women. In men, individuals in the highest CEA quartiles had significantly increased arterial stiffness compared to the lowest serum CEA quartile. In women, arterial stiffness increased at third quartile. This association remained statistically significant after adjusted confounding factors which were known for associations with ba-PWV by previous analysis including smoking and exercise.

In nonmalignant conditions, including acute and chronic inflammation and other inflammatory-related conditions such as aging and smoking are characterized by increased CEA concentrations[2]. Previous studies have reported that elevated CEA is related with metabolic syndrome and atherosclerosis as inflammatory deriving biological properties[3-4]. Aarons et al and Gangopadhyay et al reported that CEA facilitates the process of monocytes and macrophages to release proinflammatory cytokines and activate endothelium, which induce adhesion molecules on endothelial cells[15-16]. Early phase of atherosclerosis is constituted as recruitment of inflammatory cells after induction of adhesion molecules on the surface of vascular endothelial cells[17]. Although causality is unclear, this might explain the link between increased inflammatory processes, elevated CEA and arterial stiffness. Further studies are necessary to elucidate the exact mechanism between CEA and arterial stiffness.

The mean CEA was reported to be elevated among smoking subjects[18] which was also shown in this study (Figure 1). In our previous study, smoking and ba-PWV was not correlated[19] and studies on Korean subjects showed inconsistent ba-PWV value according to smoking status[20]. However, we considered smoking as an important confounding factor so smoking status was included in all adjustment.

Resting heart rate as a parameter of autonomic tone and sympathetic/parasympathetic tone was considered as a confounding factor[21]. However, we found that CEA is related with arterial stiffness in Korean even after adjusting for vascular tone and inflammation related confounding factors, such as hs- CRP, WBC count and uric acid, which were reported to be related with arterial stiffness[19, 22]. In apparently healthy population, CEA may be useful assessment of early arterial stiffness. There are some limitations in our study. First, the causality between CEA and arterial stiffness cannot be confirmed in this cross-sectional study. Second, serum CEA is known to be elevated in chronic renal failure, passive smoking, chronic lung disease, gastrointestinal tract infection and menopause state[23-26] but we did not include those as confounding variables. Third, although serum CEA is mostly related to colon disease, out data did not provide the colonoscopy results.

V. CONCLUSION

The CEA level might be associated with arterial stiffness in Korean men and women. When the serum CEA level is slightly increased or even in normal range, we should check the possibilities of arterial stiffness in addition to the hidden malignancy. The role of CEA in arterial stiffness and optimal CEA level to prevent arterial stiffness should be further investigated.

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< ABSTRACT (IN KOREAN)>

한국인의 혈청 carcionoembryoic antigen (CEA) 수치에 따른 동맥 경직도의 변화

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배우리

배경: Carcinoembryonic antigen (CEA)는 널리 알려진 암표지자이나 최근 연구에서 동맥 경화 및 심혈관 질환도 관련이 있다고 밝혀졌다. 하지만 동맥 경직도와 CEA의 관계에 대해서는 아직 잘 알려지지 않았다. 따라서 본 연구는 한국인 성인에서 상완-발목 맥파 속도로 측정한 동맥 경직도와 혈청 CEA 수치가 관련이 있는지에 대한 분석을 시행하였다.

방법: 정기 건강 검진을 받으러 내원한 총 2909명(남자 1676명, 여자 1142명)의 대상군을 혈청 CEA 수치에 따라 사분위수로 나누었다: 남자는 Q1 (CEA < 1.3 mg/dl), Q2 (1.3 mg/dl ≤ CEA ≤ 1.8 mg/dl), Q3 (1.9 mg/dl ≤ CEA ≤2.6 mg/dl), Q4 (2.7 mg/dl < CEA)로 분리하였고 여자는 Q1 (CEA < 1.0 mg/dl), Q2 (1.0 mg/dl ≤ CEA ≤ 1.3 mg/dl), Q3 (1.4 mg/dl ≤ CEA ≤1.9 mg/dl), Q4 (2.0 mg/dl < CEA) 로 분리하였다.

결과: 사분위수가 증가함에 따라 평균 상완-발목 맥파 속도도 점차 증가하였다. 연관된 변수를 보정한 후에도 상완-발목 맥파 속도는 혈청 CEA와 독립적으로 유의한 관계를 나타냈다 (P< 0.001). 높은 상완-발목 맥파 속도 (75 백분위수 이상; 남자 1518 cm/s, 여자 1487 cm/s)를 나타내는 odds ratio는 남자에서 1.00 (Q1), 1.044(0.659-1.652, Q2), 1.075(0.688-1.681, Q3), 1.595(1.009-2.520, Q4), 여자에서 1.00 (Q1), 1.719(0.971-3.032, Q2), 1.793(1.019-3.156, Q3), 2.330(1.312-4.139, Q4)로 확인되었다 (P< 0.001).

결론: 한국인 성인에서 혈청 CEA수치는 상완-발목 맥파 속도로 측정한 동맥 경직도와 연

관이 있다. 따라서 혈청 CEA 수치가 높을 시 대장 질환뿐만 아니라 동맥 경화의 가능성도 염두에 두어야 하겠다.

핵심되는 말: carcinoembryonic antigen, 동맥 경직도, 상완-발목 맥파 속도