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Cigarette Smoking in Men and Women and Electronic Cigarette Smoking in Men are Associated with Higher Risk of Elevated Cadmium Level in the Blood

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ABSTRACT

Background: We investigated the association between blood concentration of cadmium and smoking status including use of electronic cigarettes (E-cigars).
Methods: We used data from the Korea National Health and Nutritional Survey 2013 and 2016. A total of 4,744 participants (2,162 men and 2,582 women) were included and were categorized into five groups (Non-smokers, E-cigar non-users in past-smokers, E-cigar users in past-smokers, E-cigar non-users in cigarette-smokers and E-cigar users in cigarette-smokers). Cadmium blood concentration was categorized into tertiles. All sampling and weight variables were stratified, and analysis to account for the complex sampling design was conducted.
Results: In both genders, the geometric cadmium concentration was significantly different according to smoking status (both genders, analysis of variance *P* value < 0.001). In men, E-cigar users were significantly higher than the non-smokers (*P* value = past-smokers, 0.017; cigarette-smokers, < 0.001) when fully adjusted. Compared with non-smokers, fully-adjusted odds ratios (95% confidence intervals) for the highest cadmium tertiles of E-cigar non-users in cigarette-smokers and E-cigar users in cigarette-smokers were 6.56 (3.55–12.11) and 5.68 (1.96–16.50) in men and 2.74 (1.42–5.29) and 1.29 (0.10–17.44) in women.
Conclusion: Conventional cigarette smoking in men and women and E-cigar use in men are associated with higher risk of elevated blood cadmium level. Preventive management of cadmium exposure monitoring in conventional cigarette-smokers and E-cigar users may be needed.

Keywords: Cadmium; Electronic Cigarette; Smoking; Tobacco

INTRODUCTION

Cadmium is a ubiquitous metallic toxin that naturally occurs in components of the earth's crust and waters. The general population ingests a low-level of cadmium daily through food. Cigarette smoking is one of the most common sources of cadmium,[1] which accumulates in the human kidneys, liver, and testes, where it has a half-life of about 10 to 30 years.

Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Lee JW, Kang HT. Data curation: Lee JW, Kim YS, Kim YH, Yoo HS. Formal analysis: Lee JW, Kim YH. Methodology: Lee JW, Kim YS. Writing - original draft: Lee JW, Yoo HS. Writing - review & editing: Lee JW, Kang HT.

Chronic cadmium exposure produces toxic effects in the kidneys, bone, and circulatory and respiratory systems.[2-4] Blood concentration of cadmium, even at a level below current safety standards, is associated with an increased prevalence of peripheral arterial disease.[5] The International Agency for Research on Cancer (IARC) Monographs warned that cadmium and its compounds are Category 1 carcinogens.[6] A recent meta-analysis supported the IARC's warning that low-level environmental exposure to cadmium increases the risk for all cancers, and lung cancer specifically.[7]

Tobacco smoke is an important source of cadmium exposure. About 0.5–2 μg of cadmium is contained in one cigarette, and about 10% of the cadmium content is inhaled when smoking a cigarrette.[1,8,9] Because of its long half-life, cadmium gradually accumulates in the smoker's body and may have harmful effects. Smokers generally have a higher level of cadmium than non-smokers. The United States Food and Drug Administration (FDA) has classified cadmium as one of 93 harmful and potentially harmful constituents (HPHCs) in tobacco products and associated smoke. In addition, the FDA defined cadmium as a carcinogen and cardio-pulmonary toxicant.[10]

Electronic cigarettes (E-cigars) are an electronic nicotine delivery system that contains many trace constituents due to thermal degradation of tobacco-derived nicotine.[11] The FDA recommends reporting HPHC levels, including those of cadmium, in E-cigar liquids and aerosols.[12] Several studies[13-15] have demonstrated that the concentration of cadmium in the aerosol from E-cigars is lower than that of tobacco smoke. However, few studies have investigated the blood cadmium concentration in E-cigar smokers. If E-cigar smokers have a higher blood concentration than non-smokers, long-term use of E-cigar may cause harmful health effects.

The purpose of this study was to determine if a difference exists in cadmium blood concentration according to smoking status, including use of E-cigars, using the Korea National Health and Nutritional Survey (KNHANES).

METHODS

Data source

We used data from KNHANES, a cross-sectional and nationally representative survey conducted by the Korea Centers for Disease Control and Prevention (KCDC) based on the National Health Promotion Act. Detailed information about KNHANES has been published in a previous study by KCDC.[16,17] To obtain a representative sample of the Korean population, KNHANES used a complex and multi-step probability sample design. This survey consisted of data about health status, health behavior, socioeconomic demographics, and laboratory tests obtained by trained interviewers in face-to-face interviews with participants.

Study population

The data for this study were derived from questionnaires on E-cigars that have been conducted since 2013, as well as cadmium concentrations surveyed in 2013 and 2016. From a total of 16,168 subjects, 4,744 participants (2,162 men and 2,582 women) were included in this study after excluding individuals younger than 20 years of age and those with missing values for cadmium and smoking on questionnaires.

Measurements

Blood samples were collected from the antecubital vein in the morning after an overnight fast. Cadmium was measured by the graphite furnace atomic absorption spectrometry (GF AAS) method using a Perkin Elmer AAnalyst 600 (PerkinElmer, Waltham, MA, USA). Fasting plasma glucose and cholesterol were measured using a Hitachi Automatic Analyzer 7600-210 (Hitachi, Tokyo, Japan). Blood pressure was measured by a special investigator using a standard mercury sphygmomanometer (Baumanometer; Baum Co, Inc., Copiague, NY, USA).

Definition of variables including smoking status

Information on health-related lifestyles was obtained from data gathered using a self-reported questionnaire. Participants were categorized into non-, past-, and cigarette-smoker groups. Those who answered "Yes" to "Have you ever smoked an electronic cigarette during the last month?" were classified as E-cigar users. We subdivided smoking and E-cigar users into smaller groups (E-cigar non-users in past-smokers, E-cigar users in past-smokers, E-cigar non-users in cigarette-smokers and E-cigar users in cigarette-smokers). Cigarette-smokers were asked for the number of cigarettes smoked per day and smoking duration, and past-smokers reported the age at which they quit smoking and the number of cigarettes smoked per day before quitting. From these reports, we calculated pack-years of cigarettes smoked. The participants were divided into three groups according to cadmium blood concentration: T_1, 0–0.6413 (men), 0–0.8139 (women); T_2, 0.6413–1.0534 (men), 0.8139–1.3090; T_3, more than 1.0534 (men), more than 1.3090 (women).

Monthly average household income was calculated by dividing total monthly house income by the square root of the number of family members. Individuals who engaged in moderate physical activity for more than 150 minutes per week or in vigorous physical activity more than 75 minutes per week were defined as the sufficient physical activity group. Men who drank more than 7 cups of alcohol and women who drank more than 5 cups more than twice a week were categorized as heavy alcohol-drinkers. Occupational status was classified into manual workers (clerks; service and sales workers; skilled agricultural, forestry, and fishery workers; persons who operate or assemble crafts, equipment, or machines; and elementary workers), office workers (general managers, government administrators, professionals, and basic office workers), and others (unemployed persons, housekeepers, and students). Educational status was divided into four groups: elementary school or less (education duration less than 6 years), middle school (education duration between 6 and < 9 years), high school (education duration between 9 and < 12 years), and college or more (education duration 12 years or more). Marital status was categorized into "married and not separated" and "single," which included not married, separated, divorced, and widowed individuals. Chronic diseases included hypertension, diabetes, dyslipidemia, and cardiovascular/cerebrovascular disease.

We selected the confounding variables that could be analyzed in KNHANES by referencing previous studies.[18-22] Continuous variables were stratified and analyzed for differences in cadmium blood concentrations between groups. Body mass index was stratified by 25 kg/m^2, cholesterol by 250 mg/dL, glucose by 126 mg/dL, and systolic blood pressure by 140 mmHg, respectively.

Statistical analysis

All data for continuous variables are presented as mean ± standard error (SE). Data for categorical variables are presented as percentage ± SE. All sampling and weight variables

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were stratified. The SAS survey was used for statistical analysis to account for the complex sampling design and to provide nationally representative prevalence estimates. *P* values were determined by analysis of variance (ANOVA) analysis for the continuous variables or χ^2 test for categorical variables with weighting of survey design according to smoking status. We calculated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using multivariate logistic regression analysis to investigate factors associated with high cadmium according to gender. Because blood cadmium concentrations have skewed distributions, we analyzed the concentrations using log-transformation. To compare the geometric mean concentration of cadmium, we performed ANOVA with adjustment for age, pack-years, cholesterol, glucose, systolic blood pressure, alcohol consumption, physical activity, chronic disease, income, marital status, occupation, and education status. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Two-tailed *P* values < 0.05 were considered statistically significant.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board (IRB) of Chungbuk National University Hospital (IRB No. CBNUH 2019-09-004).

RESULTS

Supplementary Table 1 describes participant characteristics after stratification by gender. The unweighted numbers of men and women were 2,162 and 2,582, respectively. The mean age was 45.7 years in men and 47.3 years in women. E-cigar users represented 2.9% of men and 0.3% of women, respectively.

Participant characteristics according to smoking status are shown in **Table 1**. E-cigar users among past-smokers made up 0.6% and 3.3% of men and women, respectively. Among cigarette smokers, E-cigar users made up 6.6% and 2.4% of men and women, respectively. In both genders, age, pack-years, body mass index, cholesterol, glucose, systolic blood pressure, household income, marital status, education status, occupation, alcohol consumption, and chronic diseases differed according to smoking status. **Table 2** presents the blood geometric mean concentrations of cadmium by general characteristics according to smoking status. There were significant differences in all variables except body mass index.

Fig. 1 shows the blood geometric mean concentration of cadmium according to smoking status. In both genders, the geometric cadmium concentration differed significantly according to smoking status (both genders, ANOVA *P* value < 0.001). Levels in men E-cigar users were significantly higher than in non-smokers (*P* value = past-smokers, 0.017; cigarette smokers, < 0.001) when adjusted by age, pack-years, cholesterol, glucose, systolic blood pressure, alcohol consumption, physical activity, chronic disease, income, marital, occupation, and education status. In women, cadmium levels were not significantly higher in E-cigar users than non-smokers.

Table 3 summarizes multivariate logistic regression analyses for the highest tertile group (T_3) according to smoking status. Compared with non-smokers, fully adjusted ORs (95% CIs) for T_3 of E-cigar non-users in past-smokers, E-cigar users in past-smokers, E-cigar non-users in cigarette smokers, and E-cigar users in cigarette smokers were 1.55 (0.84–2.88), 1.26 (0.18–

Table 1. Participants' characteristics according to smoking status by gender

Variables	Non-smokers	Past-smokers	Cigarette-smokers	*P* value
Gender, men				
Unweighted No.	531	787	844	
Age, yr	41.8 ± 0.8	51.7 ± 0.5	43.6 ± 0.5	< 0.001
Pack-years of cigarettes smoked, mean	0	16.7 ± 0.66	18.2 ± 0.8	< 0.001
BMI, kg/m^2	24.4 ± 0.2	24.6 ± 0.1	24.3 ± 0.1	< 0.001
Cholesterol, mg/dL	187.6 ± 1.8	190.1 ± 1.4	190.1 ± 1.6	< 0.001
FPG, mg/dL	98.2 ± 0.9	103.7 ± 1.0	101.4 ± 0.9	< 0.001
SBP, mmHg	118.5 ± 0.7	120.7 ± 0.6	118.3 ± 0.6	< 0.001
Household income,[a] 10^4 KRW	435 ± 16	421 ± 13	403 ± 12	< 0.001
Marital status,[b] %				< 0.001
Married and not separated	97.7 ± 0.8	94.6 ± 0.9	91.4 ± 1.2	
Single	2.3 ± 0.6	5.4 ± 0.9	8.6 ± 1.2	
Education duration, yr, %				< 0.001
< 6	9.4 ± 1.3	13.0 ± 1.2	9.0 ± 1.0	
≥ 6 and < 9	6.7 ± 1.2	12.1 ± 1.4	9.1 ± 1.1	
≥ 9 and < 12	35.2 ± 2.5	32.3 ± 2.1	44.9 ± 2.0	
≥ 12	48.7 ± 2.6	42.8 ± 2.1	37.0 ± 2.1	
Occupation,[c] %				< 0.001
Office workers	31.8 ± 2.6	30.6 ± 2.1	27.3 ± 1.8	
Manual workers	35.9 ± 2.5	45.1 ± 2.3	52.7 ± 2.1	
Others	32.3 ± 2.5	24.3 ± 1.9	20.0 ± 1.7	
Sufficient physical activity,[d] %	54.9 ± 3.8	49.4 ± 2.7	46.2 ± 2.7	0.144
Heavy alcohol-drinking,[e] %	7.9 ± 1.3	20.9 ± 1.7	28.5 ± 1.6	< 0.001
Chronic diseases,[f] %	21.7 ± 1.9	33.0 ± 2.1	19.2 ± 1.5	< 0.001
E-cigar users, %	0	0.6 ± 0.3	6.6 ± 1.0	< 0.001
Gender, women				
Unweighted No.	2,318	125	139	
Age, yr	48.0 ± 0.4	38.2 ± 1.4	42.9 ± 1.2	< 0.001
Pack-years of cigarettes smoked, mean	0	2.3 ± 0.5	7.7 ± 0.8	< 0.001
BMI, kg/m^2	23.5 ± 0.1	22.5 ± 0.5	23.9 ± 0.4	< 0.001
Cholesterol, mg/dL	192.8 ± 0.9	189.1 ± 3.4	190.7 ± 4.0	< 0.001
FPG, mg/dL	98.7 ± 0.6	92.6 ± 1.2	97.2 ± 1.9	< 0.001
SBP, mmHg	115.3 ± 0.5	109.1 ± 1.1	113.0 ± 1.2	< 0.001
Household income,[a] 10^4 KRW	413 ± 9	384 ± 26	289 ± 18	< 0.001
Marital status,[b] %				0.007
Married and not separated	84.4 ± 0.9	85.2 ± 4.2	71.7 ± 4.1	
Single	15.6 ± 0.9	14.8 ± 4.2	28.3 ± 4.1	
Education duration, yr, %				< 0.001
< 6	21.9 ± 1.0	11.4 ± 3.1	16.6 ± 3.1	
≥ 6 and < 9	9.4 ± 0.7	7.6 ± 3.1	18.4 ± 3.4	
≥ 9 and < 12	34.2 ± 1.2	38.1 ± 5.2	49.1 ± 4.4	
≥ 12	34.5 ± 1.3	42.8 ± 4.4	15.9 ± 3.4	
Occupation,[c] %				0.026
Office workers	21.6 ± 1.1	27.5 ± 4.0	13.8 ± 3.2	
Manual workers	30.0 ± 1.3	22.2 ± 3.8	40.8 ± 4.6	
Others	48.4 ± 1.3	50.3 ± 5.0	45.4 ± 4.6	
Sufficient physical activity,[d] %	46,6 ± 1.8	40.1 ± 6.7	31.1 ± 5.5	0.060
Heavy alcohol-drinking,[e] %	3.1 ± 0.4	13.7 ± 3.5	25.9 ± 3.3	< 0.001
Chronic diseases,[f] %	25.0 ± 1.0	8.5 ± 2.9	19.4 ± 3.5	< 0.001
E-cigar users, %	0	3.3 ± 2.4	2.4 ± 1.0	0.001

All data are presented as mean ± standard errors or % ± standard errors. *P* values were determined by analysis of variance (ANOVA) for continuous variables or χ^2 test for categorical variables with weighting of survey design.
BMI = body mass index, FPG = fasting plasma glucose, SBP = systolic blood pressure, E-cigar = electronic cigarette.
[a]Household income: total monthly house income/square root of number of family members; [b]Marital status: married and not separated, single (not married, separated, divorced, widowed); [c]Occupation: office workers (general managers, government administrators, professionals, and office workers), manual workers (clerks; service and sales workers; skilled agricultural, forestry, and fishery workers; persons who operate or assemble crafts, equipment, or machines; and elementary workers), others (unemployed persons, housekeepers, and students); [d]Sufficient physical activity: moderate-intensity activity ≥ 150 minutes /week or vigorous activity ≥ 75 minutes/week; [e]Heavy alcohol-drinking: more than 7 cups for men and 5 cups for women more than twice a week; [f]Chronic diseases: self-reported hypertension, diabetes, dyslipidemia, cardiovascular, or cerebrovascular disease.

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8.63), 6.56 (3.55–12.11) and 5.68 (1.96–16.50), respectively, in men, and 0.67 (0.34–1.31), 6.31 (0.20–19.02), 2.74 (1.42–5.29) and 1.29 (0.10–17.44), respectively, in women.

Table 2. Blood geometric mean concentrations of cadmium by general characteristics of the study subjects

Variables	Non-smokers	Past-smokers		Cigarette-smokers		*P* value
		E-cigar non-users	E-cigar users	E-cigar non-users	E-cigar users	
Unweighted No.	2,849	903	9	926	57	
Geometric mean	0.89 ± 0.01	0.80 ± 0.02	0.89 ± 0.10	1.06 ± 0.02	0.91 ± 0.08	0.031
Pack-years of cigarettes smoked	N/E	14.86 ± 0.63	18.51 ± 5.89	17.31 ± 0.84	13.95 ± 2.23	< 0.001
Age, yr						
≥ 20 and < 40	0.55 ± 0.01	0.57 ± 0.02	0.83 ± 0.10	0.84 ± 0.02	0.73 ± 0.07	< 0.001
≥ 40 and < 65	1.11 ± 0.01	0.85 ± 0.02	1.07 ± 0.30	1.24 ± 0.03	1.33 ± 0.12	< 0.001
≥ 65	1.28 ± 0.03	1.08 ± 0.03	N/E	1.32 ± 0.08	2.05 ± 0.14	< 0.001
P value	< 0.001	0.024	0.836	< 0.001	< 0.001	
Gender						
Men	0.56 ± 0.02	0.79 ± 0.02	0.74 ± 0.05	1.04 ± 0.02	0.90 ± 0.06	0.090
Women	1.01 ± 0.01	0.86 ± 9.94	1.11 ± 0.12	1.19 ± 0.07	1.12 ± 0.13	0.003
P value	0.718	0.010	0.477	0.003	0.599	
BMI, kg/m^2						
≥ 25	0.94 ± 0.03	0.78 ± 0.02	0.55 ± 0.02	0.93 ± 0.14	1.06 ± 0.03	0.050
< 25	0.86 ± 0.02	0.81 ± 0.02	0.97 ± 0.07	0.90 ± 0.06	1.05 ± 0.03	0.070
P value	0.080	< 0.001	< 0.001	0.679	0.049	
Cholesterol, mg/dL						
≥ 250	1.02 ± 0.05	0.78 ± 0.07	N/E	1.28 ± 0.08	0.92 ± 0.07	0.014
< 250	0.88 ± 0.01	0.80 ± 0.02	0.89 ± 0.09	1.22 ± 0.03	0.80 ± 0.26	0.026
P value	0.691	0.011	0.418	0.013	0.508	
FPG, mg/dL						
≥ 126	1.10 ± 0.05	0.89 ± 0.04	N/E	1.24 ± 0.08	1.23 ± 0.32	0.002
< 126	0.87 ± 0.01	0.79 ± 0.02	0.89 ± 0.09	1.04 ± 0.02	0.90 ± 0.06	0.062
P value	0.037	0.006	0.418	0.001	0.569	
SBP, mmHg						
≥ 140	1.17 ± 0.04	0.95 ± 0.06	N/E	1.58 ± 0.17	1.90 ± 0.59	0.001
< 140	0.86 ± 0.01	0.79 ± 0.02	0.89 ± 0.09	1.19 ± 0.03	0.89 ± 0.06	0.105
P value	< 0.001	0.412	0.418	0.001	0.045	
Household income						
Lowest	0.90 ± 0.03	0.87 ± 0.03	1.16 ± 0.21	1.14 ± 0.04	1.02 ± 0.11	0.001
Middle-lowest	0.86 ± 0.02	0.85 ± 0.03	1.04 ± 0.03	1.01 ± 0.04	1.30 ± 0.22	0.873
Middle-highest	0.88 ± 0.02	0.80 ± 0.03	N/E	1.08 ± 0.05	0.79 ± 0.06	0.074
Highest	0.91 ± 0.03	0.71 ± 0.03	0.54 ± 0.01	0.98 ± 0.04	0.67 ± 0.10	0.653
P value	0.002	< 0.001	< 0.001	0.652	0.043	
Marital status, %						
Married and not separated	1.01 ± 0.02	0.84 ± 0.02	0.93 ± 0.09	1.13 ± 0.03	1.07 ± 0.09	< 0.001
Single	0.67 ± 0.02	0.65 ± 0.04	0.96 ± 0.13	0.94 ± 0.04	0.81 ± 0.07	0.101
P value	< 0.001	< 0.001	0.539	0.099	0.063	
Education duration, yr, %						
< 6	1.26 ± 0.03	1.03 ± 0.04	1.21 ± 0.00	1.28 ± 0.07	2.03 ± 0.33	< 0.001
≥ 6 and < 9	1.20 ± 0.05	1.01 ± 0.04	1.14 ± 0.12	1.30 ± 0.08	1.37 ± 0.08	< 0.001
≥ 9 and < 12	0.83 ± 0.02	0.79 ± 0.02	0.93 ± 0.06	1.06 ± 0.03	0.93 ± 0.09	0.060
≥ 12	0.72 ± 0.02	0.70 ± 0.02	0.66 ± 0.08	0.94 ± 0.03	0.80 ± 0.08	0.053
P value	< 0.001	< 0.001	0.060	0.053	0.066	
Occupation, %						
Office workers	0.73 ± 0.02	0.69 ± 0.03	0.66 ± 0.08	0.96 ± 0.03	1.08 ± 0.11	0.271
Manual workers	0.97 ± 0.03	0.83 ± 0.02	1.14 ± 0.09	1.11 ± 0.03	1.04 ± 0.09	0.004
Others	0.92 ± 0.02	0.87 ± 0.03	0.82 ± 0.00	1.07 ± 0.05	0.78 ± 0.09	0.221
P value	0.001	< 0.001	< 0.001	0.003	0.046	
Sufficient physical activity, %						
Yes	0.86 ± 0.03	0.87 ± 0.03	0.59 ± 0.04	1.13 ± 0.05	1.02 ± 0.08	0.584
No	1.00 ± 0.03	0.99 ± 0.03	0.96 ± 0.12	1.28 ± 0.04	1.17 ± 0.17	0.001
P value	< 0.001	0.005	0.002	0.584	0.365	

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Table 2. (Continued) Blood geometric mean concentrations of cadmium by general characteristics of the study subjects

Variables	Non-smokers	Past-smokers		Cigarette-smokers		*P* value
		E-cigar non-users	E-cigar users	E-cigar non-users	E-cigar users	
Heavy alcohol-drinking, %						
Yes	0.79 ± 0.07	0.80 ± 0.03	0.79 ± 0.05	1.15 ± 0.03	1.29 ± 0.17	< 0.001
No	0.89 ± 0.01	0.80 ± 0.02	1.00 ± 0.11	1.02 ± 0.03	0.84 ± 0.06	0.411
P value	0.004	< 0.001	0.140	< 0.001	0.068	
Chronic diseases, %						
Yes	1.20 ± 0.03	0.92 ± 0.03	1.21 ± 0.00	1.32 ± 0.05	1.37 ± 0.14	< 0.001
No	0.80 ± 0.01	0.75 ± 0.02	0.87 ± 0.09	1.00 ± 0.02	0.86 ± 0.06	0.962
P value	< 0.001	0.006	< 0.001	< 0.001	0.040	

All data are presented as geometric mean ± standard errors.
P values were determined by analysis of variance analysis with weighting of survey design.
BMI = body mass index, FPG = fasting plasma glucose, SBP = systolic blood pressure, E-cigar = electronic cigarette.

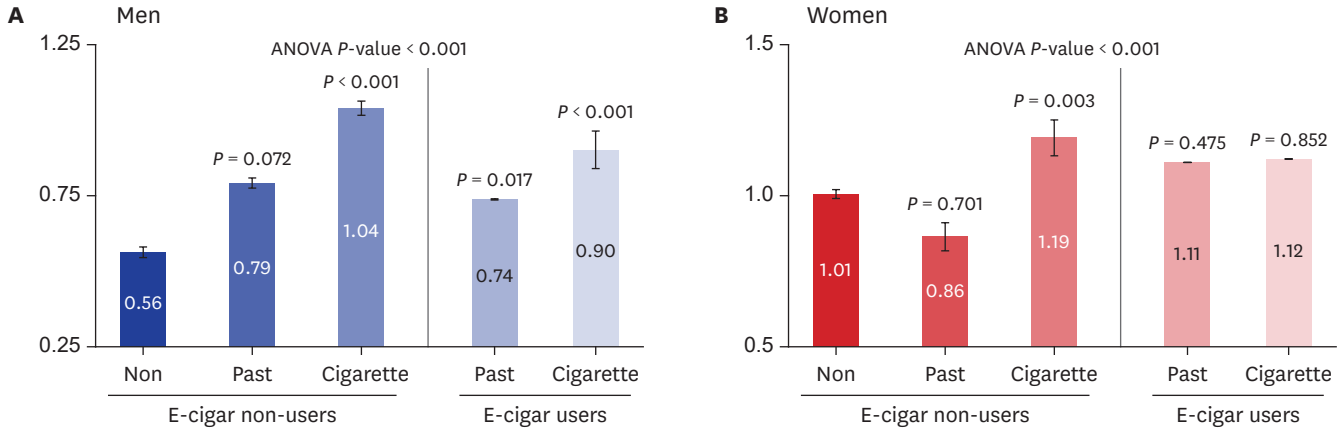

Fig. 1. Blood geometric mean concentration of cadmium according to smoking status. (**A**) Men. (**B**) Women. Values among smoking status groups were compared using ANOVA adjusted for age, pack-years, cholesterol, glucose, systolic blood pressure, alcohol consumption, physical activity, chronic disease, income, marital status, occupation, and education status.
P values were calculated by comparing each group with the non-smoker group adjusted for multiple variables.
ANOVA = analysis of variance, E-cigar = electronic cigarette.

Table 3. Odds ratio for high cadmium group according to smoking status

Variables	Non-smokers	Past-smokers		Cigarette-smokers	
		E-cigar non-users	E-cigar users	E-cigar non-users	E-cigar users
Men					
MODEL 1	Reference	1.68 (0.89–3.16)	1.70 (0.30–10.44)	7.51 (4.10–13.73)	7.35 (2.54–21.30)
MODEL 2	Reference	1.63 (0.88–3.04)	1.24 (0.18–8.29)	7.02 (3.83–12.89)	7.07 (2.43–20.57)
MODEL 3	Reference	1.55 (0.84–2.88)	1.26 (0.18–8.63)	6.56 (3.55–12.11)	5.68 (1.96–16.50)
Women					
MODEL 1	Reference	0.62 (0.32–1.22)	6.22 (0.18–22.52)	2.76 (1.48–5.16)	1.23 (0.12–13.30)
MODEL 2	Reference	0.62 (0.31–1.22)	5.67 (0.17–19.08)	2.70 (1.41–5.17)	1.21 (0.12–12.80)
MODEL 3	Reference	0.67 (0.34–1.31)	6.31 (0.20–19.02)	2.74 (1.42–5.29)	1.29 (0.10–17.44)

Odds ratios and 95% confidence intervals were calculated using weighted multivariate logistic regression analyses.
MODEL 1: Adjusted for age, pack-years; MODEL 2: MODEL 1 + cholesterol, glucose, systolic blood pressure, alcohol consumption, physical activity, and chronic disease; MODEL 3: MODEL 2 + Income, marital, occupation, and education status; High cadmium group: in the upper tertile (> 66%).

DISCUSSION

Using nationally representative data, we found that the blood concentration of cadmium varied according to smoking status. In both genders, the geometric cadmium concentration was significantly different according to smoking status. Levels in men E-cigar users were significantly higher than in non-smokers. Compared to non-smokers, adjusted ORs for T_3 for

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both E-cigar non-users and E-cigar users among cigarette smokers increased in men, while only the OR for E-cigar non-users in cigarette smokers was significantly higher in women.

Previous studies have shown that current smokers have higher blood cadmium concentrations than non-smokers.[1,8,9,18,19,23] According to a literature review by Järup et al.,[19] the blood cadmium level in non-smokers is usually lower than 0.5 μg/L, while that for current-smokers is as high as 1–4 μg/L, which is similar to our findings. Smoking one pack of cigarettes per day (20 cigarettes) would result in daily retention of about 1 to 2 μg/L of cadmium.[1,8,9,18] Cadmium retention from daily food intake is estimated to be about 0.75 to 1 μg/L.[18] or about half of the exposure from smoking. Previous autopsy studies[24,25] have shown that smokers have about twice the cadmium content in most of their tissues as non-smokers. These previous studies conclude that conventional cigarette smoking is significantly associated with a higher cadmium accumulation in the human body.

In addition to conventional smoking, we hoped to investigate whether or not E-cigar smoking was positively related to higher cadmium retention. We found that geometric mean concentrations of cadmium in E-cigar users were significantly higher than in non-smokers among men after fully adjusting the comparison (**Fig. 1**). In men E-cigar users among cigarette smokers, the fully adjusted OR for T_3 was high at 5.68 (1.96–16.50) compared with the non-smoker group. There have been few reports on blood cadmium level in E-cigar smokers. In one recent study,[20] the geometric mean blood cadmium concentration of E-cigar smokers was lower than that of conventional cigarette smokers (0.44 [0.37–0.52] μg/L in E-cigar smokers vs. 1.44 [1.16–1.78] in conventional cigarette smokers). However, that study included a relatively small number of 146 volunteer participants who may not represent the general population. According to other previous studies,[13-15] the amount of toxic substances contained in E-cigar aerosols is less than that of conventional cigarettes. For this reason, E-cigars are often considered a less harmful alternative to conventional cigarettes.

However, recent studies[26-28] claim that some metal concentrations in E-cigar aerosols may be higher than in conventional cigarettes because the metallic components are sensitive to cyclic temperature changes. E-cigar devices consist mainly of the battery and the atomizer, which includes a chamber and head. The atomizer chamber is generally composed of metal, plastic and/or glass in which the E-cigar liquid is stored. The atomizer head consists of a wick and metal coil, which is responsible for the heat transfer to the liquid that is subsequently evaporated. This structure allows some metallic components to be delivered to the aerosol.[29]

After chronic exposure for several months, cadmium blood concentration reaches an equilibrium state, and cadmium is steadily excreted through the urinary tract. Therefore, blood and urine concentrations of cadmium indicate recent and chronic exposure to cadmium, respectively.[1,19,21] For this reason, blood cadmium concentration might be more useful in assessing the harmful effects of cadmium in the human body than measurement of E-cigar aerosols. In this study, the blood cadmium geometric concentration of E-cigar users (those who had smoked E-cigars within one month) were significantly higher than those of non-smokers in men in a fully adjusted analysis. This finding could be interpreted to mean that E-cigar users among the men were recently exposed to cadmium. The toxic effects of E-cigars remain controversial due to a lack of long-term clinical evidence about whether or not E-cigars are harmful.[26] More studies are needed to investigate the harmful effects of E-cigars on human health.

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This study has several potential limitations. First, causality could not be demonstrated because this study had a cross-sectional design without follow-up. However, a reverse causal relationship is not logical because high cadmium concentrations do not facilitate cigarette smoking. Second, because the data of this study are based on self-reported questionnaires, we could not exclude the possibility of reporting bias. Therefore, the actual number of E-cigar and conventional cigarette smokers might be underestimated, especially among women. In addition, because the E-cigar users group was defined as those with experience smoking an E-cigar within one month, this group might not be representative of daily E-cigar users. Furthermore, the number of women smokers was too small to demonstrate a statistically significant difference when compared to the large number of women non-smokers. Third, this study did not discriminate among various kinds of E-cigar devices and liquids. Because the secondary data from KNHANES were used, we could not further stratify for E-cigar types. In particular, heat-not-burn tobacco, which is rapidly increasing worldwide,[30,31] has not been considered as a data acquisition problem. Fourth, because the E-cigar users group was relatively small, there is a possibility of selection bias.

Despite these limitations, this study has several strengths. Above all, our study was derived from a population-based sample with a complex survey design that sought to generate estimates representative of the Korean population. In addition, this is the first Korean study to investigate the blood cadmium level of E-cigar users using nationally representative data. Second, smoking status was categorized into five groups including E-cigar users. Third, the use of blood concentration of cadmium was also a strength of the study.

In conclusion, the blood geometric concentration of cadmium varied according to smoking status in both genders. Conventional cigarette smoking in men and women and E-cigar use in men was associated with a higher risk of elevated blood cadmium level. Conventional tobacco and E-cigar users may have experienced recent cadmium exposure with potentially harmful health effects. Preventive management using cadmium exposure monitoring in conventional cigarette smokers and E-cigar users is needed.

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Participants' characteristics

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