Coffee Intake and Trace Element Blood Concentrations in Association with Renal Cell Cancer Among Smokers

Hongke Wu (✉ huw347@psu.edu)

Penn State College of Medicine <https://orcid.org/0000-0003-1835-4600>

Stephanie J. Weinstein

National Cancer Institute Division of Cancer Epidemiology and Genetics

Lee E. Moore

National Cancer Institute Division of Cancer Epidemiology and Genetics (ret)

Demetrius Albanes

National Cancer Institute Division of Cancer Epidemiology and Genetics

Robin Taylor Wilson

Temple University College of Public Health

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Coffee Intake and Trace Element Blood Concentrations in Association with Renal Cell Cancer among Smokers

Hongke Wu · Stephanie Weinstein · Lee E Moore ·
Demetrius Albanes · Robin Taylor Wilson

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Abstract Purpose: Determine whether higher coffee intake may reduce the risk of renal cell cancer (RCC) associated with lead (Pb) and other heavy metals with known renal toxicity. Methods: We conducted a nested case-control study of male smokers (136 RCC cases and 304 controls) within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Cases diagnosed with RCC at five or more years following cohort enrollment, were matched to controls on age (± 7 years) and whole blood draw date (± 30 days). Conditional logistic regression (using two-sided tests) was used to test for main effects and additive models of effect modification. Results: After a mean follow-up of 16.3 years, coffee consumption was not significantly associated with renal cell cancer risk, when adjusting for blood concentrations of Cd, Hg and Pb and RCC risk factors (age, smoking, BMI, and systolic blood pressure) (p-trend, 0.134). The association with above median blood Pb and RCC (HR = 1.69, 95% CI: 1.06, 2.85) appeared to be modified by coffee consumption, such that RCC risk among individuals with both increased coffee intake and higher blood lead concentration was nearly 3-fold higher RCC risk (HR=3.40, 95% CI: 1.62, 7.13; p-trend 0.003). Conclusion: Contrary to our initial hypothesis, this study suggests that heavy coffee consumption may increase the previously identified association between higher circulating lead (Pb) concentrations and increased RCC risk. Improved assessment of exposure, including potential trace element contaminants in coffee, are needed.

Keywords Renal cell cancer · Heavy metals · Coffee consumption · Epidemiology

Background

Well-established risk factors for renal cell cancer (RCC) include cigarette smoking, elevated blood pressure, and obesity—explaining approximately half of all cases [1]. Other factors which have been associated with RCC include diabetes, low exercise, increased alcohol intake, lead (Pb) exposure, and some occupational exposures [3, 40, 50]. Worldwide, nearly every country has reported increases in the age-adjusted incidence of RCC over the past decade, despite relatively constant population prevalence rates of obesity, smoking and hypertension, and a greater than two-fold increase in the prevalence of controlled hypertension in some countries [50]. Taken together, this suggests the need to identify additional factors for improved RCC prevention. Coffee intake is thought to play a role in chemoprevention of cancer through antioxidant activity of naturally occurring polyphenols in coffee beans (e.g., flavonoids and chlorogenic acids) [33]. Coffee is the major dietary source of polyphenols, accounting for 40 to 45 percent of total daily intake in some populations [10, 18]. We and others have identified

Hongke Wu, MD, MPH

Department of Public Health Science, Penn State College of Medicine, Hershey, PA (ORCID: 0000-0003-1835-4600)

Stephanie Weinstein, MS, PhD

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (ORCID: 0000-0002-3834-1535)

Lee E Moore, PhD, MPH

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (ORCID: 0000-0001-7317-910X)

Demetrius Albanes, MD

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (ORCID: 0000-0001-8330-4293)

Robin Taylor Wilson, PhD (Corresponding Author)

Department of Epidemiology and Biostatistics, Temple University College of Public Health, Philadelphia, PA (ORCID: 0000-0002-5739-558X)

Tel.: 215-204-6119

Fax: 215-204-1854

E-mail: robin.taylor.wilson@temple.edu

significantly reduced RCC risk associated with dietary intake of flavonoids, including quercetin—also found in coffee beans [49, 4]. Coffee may also act indirectly by reducing risk of other RCC risk factors. For example, a meta-analysis of observational studies suggest high coffee intake is associated with a 30% reduction in the risk of diabetes[32]. In contrast, clear cardiovascular benefits of coffee intake (which may also prevent RCC) have not been identified. Randomized trials of coffee intake have identified no decrease in systolic or diastolic blood pressure over an average treatment period of 62 days [32]. Contrary to a cardiovascular benefit, meta-analyses of randomized trials reports consistent increases in total cholesterol, LDL cholesterol and triglycerides in coffee intake intervention groups, thought to be mainly due to the diterpene content of coffee[32, 27]. Historically, high coffee intake in the United States general population has been strongly correlated with tobacco smoking (number of cigarettes per day) and blood biomarkers of Pb and cadmium (Cd) [5, 16, 8]. While Cd is not an established risk factor for RCC, this heavy metal has a half-life in the kidney of ~30 years and is a known renal toxicant[8, 36, 37]. Within high coffee intake regions, approximately 4 percent of dietary Pb intake has been attributed to coffee drinking [41]. To date, epidemiologic studies of coffee intake and RCC risk have not investigated the possibility of effect modification by exposure to heavy metals with known renal toxicity (Cd, Hg and Pb) [14]. Therefore, the purpose of this study is to determine whether higher coffee intake may reduce the risk of renal cell cancer (RCC) associated with lead (Pb) and other heavy metals with known renal toxicity among smokers in Finland. Globally, Finland ranks among the countries with the greatest per capita coffee consumption [35, 31].

Methods

Cohort Participants and Matching Criteria

We conducted a nested case-control study within the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. ATBC enrolled nearly 30,000 male smokers aged 50-69 years in southwestern Finland from 1985-1988. As previously described, the ATBC study is a randomized, double-blind, placebo-controlled primary cancer prevention trial designed to determine the efficacy of daily supplementation with alpha-tocopherol, beta-carotene, or both in preventing lung cancer or other cancers[13]. Participants were excluded from the ATBC study cohort if they smoked <5 cigarettes per day, had a prior history of cancer (other than non-melanoma skin cancer or carcinoma in situ), severe angina upon exertion, chronic renal insufficiency, liver cirrhosis, alcoholism, anticoagulant use, vitamin E supplementation (>20 mg/day), vitamin A supplementation (>20,000 IU/day), beta-carotene supplementation (>6 mg/day), or other medical conditions that would prevent them from completing the six year trial. The Finnish Cancer Registry allows for patient diagnosis tracking long-term with nearly 100% ascertainment. At baseline, all participants were measured for height, weight, and blood pressure, and completed a questionnaire containing information on dietary intake, supplement use, medical history, physical activity, and smoking history. Dietary intake was obtained using a validated 12-month food frequency questionnaire consisting of modified diet history including both portion size and frequency of consumption. Cumulative lifetime smoking exposure was estimated in pack-years, with one pack-year equal to 20 cigarettes smoked per day for one year. High risk occupations were defined as mining, colliery (coal mining), quarrying, stonemasonry, stonecutting, foundry work, asbestos quarrying, asbestos fabric manufacture, asbestos concrete manufacture, asbestos insulating, lead refining, nickel refining, copper smelting, steel production/refining, oil refining, gas manufacture, chromium paint manufacture, and arsenic production[40].

Our analysis utilized a nested case-control study of the ATBC cohort including 136 RCC cases and 304 matched controls. Cases diagnosed with RCC at least 5 years following enrollment into the ATBC study and at least 2 months after the whole blood draw were identified by linkage to the Finnish Cancer Registry and histologically confirmed as renal cell cancer (International Classification of Diseases, version 9, code 189.0) by linkage to the Finnish Cancer Registry. The medical records of the cases diagnosed through April 1999 were reviewed by one study physician to confirm the diagnosis of RCC whereas cases diagnosed after April 1999 were based solely on the Finnish Cancer Registry data, as previously described [2]. The first group of controls (n=183) were matched on age at randomization (± 7 years), whole blood draw date (± 20 days within the same season), pack-years of smoking (matched on either above or below the median of the ATBC cohort of 35 pack-years), ATBC treatment group, and time to follow-up (i.e., controls having at least as much follow-up time as matched cases). The second group of controls (n = 121) had been previously chosen for the Vitamin D Pooling Project (VDPP) and were matched on age at randomization (± 1 year), whole blood draw date (± 30 days within the same season), assuring that the control is alive and cancer free at case diagnosis date. A 12-hour fasting serum sample was collected at baseline in 1985 to 1988 and whole blood was collected near or at the final trial visit between August 1992 and March 1993. Details of study participants can be found elsewhere [40].

88 Trace Element Concentrations

89 Total whole blood concentrations of Cd, Hg and Pb were determined using inductively coupled plasma mass
90 spectrometry (ICP-MS) at the Wisconsin State Laboratory of Hygiene in Madison, WI. Study samples were
91 run in duplicate, by staff who were blinded to the case/control status of the subjects' samples. Quality control
92 samples and sample duplicate concentrations used for the study had to agree within ± 0.4 mg/L or 10%. The
93 ICP-MS assay measures both organic and inorganic isoforms of Cd, Hg and Pb.

94 Statistical analysis

95 Quantitative variables were divided into quartiles based on the distribution among controls. The number of
96 years from enrollment to cancer diagnosis was calculated as the number of days from enrollment to diagnosis
97 divided by 365.25. Differences in categorical distributions were tested by the Chi Square test, and in the event of
98 a cell size less than five, the Fisher's exact test was used. The Spearman's (nonparametric) correlation coefficient
99 was used to estimate the magnitude of the bivariate correlations between age, body mass index (BMI), coffee
100 intake (g/day), cigarettes per day, systolic blood pressure, and whole blood concentrations of Cd, Hg and Pb.
101 Crude and adjusted conditional logistic regression models were calculated using Proc PHREG in SAS.
102 Adjusted models included factors known to be associated with RCC, including age, systolic blood pressure,
103 and BMI. In the general population, whole blood Cd concentrations are most closely linked with tobacco use
104 and smokers have approximately 2-fold greater blood concentrations compared with non-smokers (NHANES)
105 [28]. In order to avoid over-adjustment for smoking by using both cigarettes per day and whole blood Cd
106 concentrations, we retained only whole blood Cd in all models in order to both test for the main effect of Cd
107 and as an adjustment variable. ATBC treatment group has been previously shown not to be associated with RCC
108 and was therefore not included in this analysis [40]. Tests for trend were conducted by regressing the quartile
109 median value, adjusting for other factors in the model. Two-way interactions were tested by multiplying the
110 continuous value of each parameter together and testing the beta statistic for the interactive variable with the
111 main effect terms in the adjusted conditional logistic regression model. Coffee intake and blood concentrations
112 of trace elements were log transformed if used as continuous variables. Tests for additive effects between whole
113 blood trace element concentrations and coffee intake were conducted by a categorical assessment of above/below
114 median combined categories (i.e., high coffee intake and high trace element intake, high coffee intake/and low
115 trace element blood concentration, etc.). All statistical tests of significance (defined as $p < 0.05$) were two-tailed.
116 All statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary NC).

117 Results

118 The mean ($\pm$ SD) total follow-up time was 16.3 years (12.1 ± 4.1 years (mean $\pm$ standard deviation) for cases
119 and 18.1 ± 3.1 years for controls, data not shown). The mean age at baseline was 56.9 years, and mean number
120 of cigarettes smoked per day was 20.1 (± 8.1). Cases were significantly more likely than controls to have a history
121 of hypertension ($p < 0.001$) and elevated systolic blood pressure ($p < 0.007$). There was no statistically significant
122 difference in BMI or matching variables (age and cigarettes per day, Table 1). Mean intake of coffee was 1.6
123 (± 0.9) cups/day, and 2.73 percent of study participants were non-coffee drinkers (data not shown).

124 Among the risk factors we investigated, the greatest positive bivariate correlations were observed between
125 number of cigarettes per day and whole blood Cd ($\rho = 0.319$, $p < 0.001$), and cigarettes per day and coffee
126 consumption (g/day) ($\rho = 0.200$, $p < 0.001$); the greatest negative correlation observed was between cigarettes
127 per day and age ($\rho = -0.197$, $p < 0.001$) (Supplemental Table 1). Notably, correlations between coffee intake
128 (g/day) and blood concentrations of Cd, Hg and Pb were not statistically significant, with all ρ below 0.05
129 (Supplemental Table 1).

130 Coffee intake was not significantly associated with RCC risk after adjusting for traditional RCC risk factors
131 (Model 1, p -trend=0.516), nor after adjusting for traditional RCC risk factors plus blood concentrations of Cd,
132 Hg and Pb (Model 2, p -trend=0.134, Supplemental Table 2). Cigarettes per day and high-risk occupations were
133 not significantly associated with RCC risk in either crude or adjusted models and therefore not included in the
134 final model (data not shown). Although the study is matched on age and pack-years of smoking, we also tested
135 these variables for an association with RCC due to the possibility of residual confounding, but left them out of
136 final models as they were not statistically significant. With respect to the main effects of trace elements (above
137 vs. below median blood concentrations of Cd, Hg and Pb), only Pb was significantly associated with RCC risk
138 (HR=1.69, 95%CI: 1.06, 2.85) (Table 2), as previously shown[40].

139 In additive tests of interaction, individuals with both above median coffee intake and above median blood
140 Pb had a significantly greater risk of RCC, (HR=3.40, 95% CI: 1.62, 7.13, $p = 0.001$), compared to individuals
141 having both below median ("low") coffee intake (< 1.5 cups/day) and below median whole blood Pb concentration

(<3.20 $\mu\text{g/dL}$), Table 3. Adjusted HR values were monotonically increasing, with increasing coffee and blood Pb (above/below median) groups (HR values=2.67, 2.68 and 3.40), and the trend was statistically significant ($p=0.003$). The test for multiplicative interaction between Pb and coffee intake was not statistically significant ($p\text{-interaction}=0.300$, data not shown). Individuals with above median coffee intake and below median blood Hg had a significantly greater risk of RCC (HR=2.00, 95%CI: 1.06, 3.77), compared to those with below median (“low”) coffee intake (<1.5 cups/day) and below median whole Hg concentration (2.70 $\mu\text{g/dL}$). There were no significant associations with RCC risk for any combination of coffee intake and blood Cd (Table 3).

Discussion

Our results suggest that high coffee intake is not protective for renal cell cancer among smokers, even after controlling for whole blood concentrations of trace elements with known kidney toxicity—i.e., Cd, Hg and Pb. There appeared to be additive effects of coffee intake with respect to high Pb blood concentrations, as higher coffee drinking (>1.5 cups per day) and higher blood Pb concentrations (>3.20 $\mu\text{g/dL}$) combined were significantly associated with the greatest magnitude of RCC risk (3.4-fold). Some studies have reported coffee intake associated with higher cadmium intake [11, 46], however we observed weak correlations between coffee intake (g/day) and blood concentrations of heavy metals (Cd, Hg or Pb) in this population of smokers.

Overall, observational epidemiologic studies are inconsistent as to whether heavy coffee intake is a risk factor or is protective against RCC development. Previous case-control studies report protective results for caffeinated coffee, no association, and elevated risk for total coffee intake, including an elevated risk for decaffeinated coffee [29, 2, 51, 12, 47]. A previous study conducted in the ATBC cohort reported no main effect association with coffee intake, and investigations in other cohorts have been similarly inconsistent – reporting both lower RCC risk and no association after 7 to 20 years of follow-up [14, 19, 21]. Large twin studies conducted in northern European populations report shared genetic factors in explaining the co-occurrence of smoking and caffeine intake, including especially caffeine intake derived from coffee drinking [42]. Part of this may be due to the fact that coffee intake is counter-indicated in some medical conditions and this may be difficult to disentangle in cohort studies when the reasons for no/reduced coffee intake is not known [7, 23, 48]. Mechanistic studies suggest that a protective association between coffee intake and RCC is biologically plausible. Genetic and epigenetic alterations in RCC tumors are well known to occur in the Von Hippel Lindau (VHL) gene and are reported in up to 80% of sporadic (non-familial) (clear cell) RCC cases [15, 24]. Multiple germline VHL mutations are associated with multiple family cancer syndromes which include RCC as a prominent feature [38]. It is likely that the results we observed in this study may be unique to heavy smokers. Nitrosamines contained in tobacco—specifically N-nitrosodimethylamine (NDMA)—influence the VHL pathway leading to DNA transversions (pyrimidine to purine changes and vice versa) [44, 39]. In contrast, compounds in coffee (i.e., flavanones) reduce tumor formation via the VHL pathway [41]. Phenolic acids and diterpenes found in coffee have been reported as potent inhibitors of cancer proliferation via the induction of apoptosis [32, 34, 30].

More recently, the acrylamide content of coffee has been brought under consideration for regulatory guidelines. An oral dose of 1 g/kg and higher to Sprague Dawley rats has been shown to induce DNA adducts within the kidney [45]. At least one cohort study of acrylamide intake has reported elevated RCC risk in humans, although not in another study [17, 26]. Coffee is one of the top three dietary contributors to total acrylamide intake in the general population [26]. Risk assessments (of both human and animal data) have set an intake limit of 1.1 g/day for a cancer risk level of 1 case per 100,000 people [45]. Further mechanistic studies are needed to better understand dose-response relationships as well as potential pathway interactions between acrylamide, nitrosamines and flavanones.

Strengths and Limitations. The major strengths of this study include a matched nested case-control design within a cohort of long-term follow-up and use of validated blood biomarkers for Hg, Cd and Pb. In addition, this study was conducted in a high-consumption cohort as Finland is among the highest per capita coffee-consuming countries. According to trade statistics, the average annual per capita consumption of coffee relevant to the time period of this cohort in Finland was 13.0 kg in 1979-83 (corresponding to 5 to 6 cups per day) [43]. Limitations of this study include the absence of information on the constituents in coffee consumed (e.g., trace elements) and coffee storage duration. Compared with stored coffee, polyphenol content of freshly roasted coffee differs by as much as 10-fold [20]. We also had no information on RCC histologic subtype which has at least nine molecular and three histologic subtypes [25]. Clear cell RCC histology, in particular, has been associated with specific mutational profiles in VHL—particularly those induced by the volatile nitrosamines, including NDMA and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [39, 6]. While N-nitroso compounds are known carcinogenic constituents of tobacco, there has been at least one incidental finding of a moderate population correlation between coffee intake and urinary N-nitrosopiperidine (NPiP) concentrations ($\rho=0.40$) in a rural population [22]. Future studies are needed that account for the mutational profile of the tumors that are known to influence these biologic pathways. We also had no information on coffee roasting, known to influence acrylamide production in coffee [9].

200 Conclusion

201 In a population of heavy smokers, this study reports a positive additive association for RCC among individuals
 202 with both high blood Pb concentrations (above 3.20 ug/dL) and higher coffee intake, after controlling for
 203 blood biomarkers of other renal toxicants (Cd and Hg). High coffee intake and high Pb combined appeared to
 204 roughly double the risk for RCC compared with Pb alone (from a HR of 1.69 to 3.40), although this study
 205 was not sufficiently powered to determine a multiplicative interaction. Improved exposure assessment of specific
 206 constituents in coffee and how they differ according to type of coffee and/or storage conditions are needed.

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327 Conflict of interest/Competing interests

328 The authors declare that they have no conflict of interest.

329 Ethics approval

330 The study did not include personal identifies and was classified as non-Human research by the Pennsylvania
331 State University IRB.

332 Consent to participate

333 All participants provided written informed consent at the time of cohort enrollment.

334 Consent to publication

335 This study has been reviewed by the Division of Cancer Epidemiology and Genetics at the National Cancer
336 Institute.

337 Availability of data and material

338 Data are available upon request and proposal approval from Demetrius Albanes, MD National Cancer Institute.

Table 1 Participant characteristics by case status and unadjusted (crude) hazard ratio (HR) results, male smokers in Finland

Variables		Controls % (N) Total=304	Cases % (N) Total=136	P-value*	Crude HR	95%CI	P-value**
Age in years, mean(Q1-Q3)		56.9 (53.0–60.0)	56.9 (53.5–60.0)	0.950	1.2	0.86, 1.55	0.328
BMI(kg/m ²)	Underweight (<18.5)	9.5(29)	2.9(4)	0.136	2.4	0.15, 39.53	0.289
	Normal (18.5 to <25)	17.8(54)	10.2(14)		Reference		
	Overweight (25 to <30)	21.7(66)	27.9(38)		1.4	0.90, 2.30	
	Obese(≥30)	51.0(155)	58.8(80)		1.7	0.90, 3.12	
Systolic Blood Pressure (mmHg)	Normal(<120)	0.3(1)	0.7(1)	0.007	Reference		0.013
	Elevated(120–129)	38.2(116)	28.7(39)		1.4	0.43, 4.80	
	Stage I(130–139)	49.0(149)	52.9(72)		3.7	1.21, 11.24	
	Stage II(140+)	12.5(38)	17.7(24)		3.3	1.11, 9.75	
History of hypertension	No	84.2(256)	72.1(98)	<0.001	Reference		0.002
	Yes	15.8(48)	27.9(38)		2.3	1.35, 3.95	
Smoking(cigarettes per day)	5 to 15	17.4(53)	19.1(26)	0.848	Reference		0.931
	16 to 20	16.8(51)	16.9(23)		0.9	0.45, 1.86	
	21 to 25	38.8(118)	34.6(47)		0.8	0.28, 1.59	
	Over 25	27.0(82)	29.4(40)		0.9	0.44, 1.94	

BMI:body mass index; N: total number; HR: hazard ratio; CI: confidence interval; Q: Quartile

* P-values were calculated in the Chi-sqaure.

** P-values were calculated in the Cox Hazard analysis.

Table 2 Risk of renal cell cancer according to median trace element blood concentrations, male smokers in Finland

Variables(median cut-off value)*		# Cases/Controls	Crude HR (95%CI)	P-value	# Cases/Controls	Adjusted HR** (95%CI)	P-value
Cadmium (Cd)	Low (<0.94 ug/dL)	65/152	Reference	0.809	59/141	Reference	0.908
	High ($\geq$ 0.94 ug/dL)	71/152	1.05 (0.70,1.58)		69/149	1.03 (0.59,1.43)	0.908
Lead (Pb)	Low (<3.20 ug/dL)	51/143	Reference	0.055	47/130	Reference	0.026
	High ($\geq$ 3.20 ug/dL)	85/161	1.55 (0.99,2.41)		81/160	1.69 (1.06,2.85)	
Mercury (Hg)	Low (<2.70 ug/dL)	74/151	Reference	0.229	68/142	Reference	0.141
	High ($\geq$ 2.70 ug/dL)	62/153	0.78 (0.52,1.17)		60/148	0.73 (0.48,1.11)	

HR: hazard ratio; CI: confidence interval

* Median cut-off values for blood concentrations of Cd, Hg and Pb are based on the median value among controls.

** Adjusted model includes body mass index, systolic blood pressure, and blood concentrations of Cd, Hg and Pb.

All cases matched to controls. The first group of control (n=183) were matched on age at randomization (± 7 years), whole blood draw date (± 20 days within the same season), pack-years of smoking (matched on either above or below the median of the ATBC cohort of 35 pack-years), ATBC treatment group, and time to follow-up (i.e., controls having at least as much follow-up time as matched cases). The second group of controls (n=121) had been previously chosen for the Vitamin D Pooling Project (VDPP) and were matched on age at randomization (± 1 year), whole blood draw date (± 30 days within the same reason), assuring that the control is alive and cancer free at case diagnosis date.

Table 3 Additive risks of renal cell cancer with respect to blood concentrations of lead (Pb), cadmium (Cd) and mercury (Hg) and daily coffee intake, male smokers in Finland

Daily Coffee Intake and Whole Blood Concentrations of Pb, Cd and Hg	Adjusted HR*	95%CI	P-value
Lead (Pb)			
Less than 1.5 cups (<550 g/day) plus below median Pb (<3.20 ug/dL)		Reference	
≥ 1.5 cups (≥550g/day) plus below median Pb (<3.20 ug/dL)	2.68	1.26,5.71	0.011
Less than 1.5 cups (<550 g/day) plus above median Pb (≥3.20 ug/dL)	2.67	1.26,5.65	0.010
≥ 1.5 cups (≥550g/day) plus below median Pb (≥3.20 ug/dL)	3.40	1.62,7.13	0.001
P-trend**			0.003
Cadmium (Cd)			
Less than 1.5 cups (<550 g/day) plus below median Cd (<0.94 ug/dL)		Reference	
≥ 1.5 cups (≥550g/day) plus below median Cd (<0.94 ug/dL)	1.85	0.94,3.65	0.076
Less than 1.5 cups (<550 g/day) plus above median Cd (≥0.94 ug/dL)	1.12	0.54,2.32	0.757
≥ 1.5 cups (≥550g/day) plus below median Cd (≥0.94 ug/dL)	1.71	0.90,3.25	0.102
P-trend**			0.308
Mercury (Hg)			
Less than 1.5 cups (<550 g/day) plus below median Hg (<2.70 ug/dL)		Reference	
≥ 1.5 cups (≥550g/day) plus below median Hg (<2.70 ug/dL)	2.00	1.06,3.77	0.032
Less than 1.5 cups (<550 g/day) plus above median Hg (≥2.70 ug/dL)	0.91	0.46,1.80	0.786
≥ 1.5 cups (≥550g/day) plus below median Hg (≥2.70 ug/dL)	1.24	0.65,2.34	0.517
P-trend**			0.654

HR: hazard ratio; CI: confidence interval

* Adjusted model includes body mass index, systolic blood pressure, and blood concentrations of Cd, Hg and Pb. All cases matched to controls. The first group of control (n=183) were matched on age at randomization (±7 years), whole blood draw date (±20 days within the same season), pack-years of smoking (matched on either above or below the median of the ATBC cohort of 35 pack-years), ATBC treatment group, and time to follow-up (i.e.,controls having at least as much follow-up time as matched cases).The second group of controls (n=121) had been previously chosen for the Vitamin D Pooling Project (VDPP) and were matched on age at randomization (±1 year), whole blood draw date (±30 days within the same reason), assuring that the control is alive and cancer free at case diagnosis date.

** P-trend calculated using the ordered values (i.e. 1,2,3, or 4) if the comparison groups.

Supplement Table 1 Bivariate Spearman rank correlations among covariates in the final model, ATBC Renal Cell Cancer nested case-control study*

Variables	BMI	Age	HRO	Pb	Hg	Cd	CPD	CI	SBP
Body Mass Index (BMI, kg/m ²)	–	0.014 (0.770)	0.029 (0.551)	–0.110 (0.022)	0.069 (0.150)	–0.074 (0.121)	–0.002 (0.959)	–0.002 (0.971)	0.188 (<.0001)
Age (in years)		–	0.022 (0.647)	–0.101 (0.034)	–0.008 (0.867)	–0.161 (0.001)	–0.197 (< .0001)	–0.111 (0.020)	0.130 (0.006)
High risk occupations (HRO)			–	0.047 (0.327)	–0.015 (0.749)	0.053 (0.267)	0.050 (0.294)	–0.019 (0.698)	0.008 (0.860)
Lead (Pb, ug/dL)				–	0.050 (0.299)	0.193 (< .0001)	0.081 (0.090)	–0.002 (0.965)	0.030 (0.524)
Mercury (Hg, ug/dL)					–	0.082 (0.086)	–0.083 (0.081)	–0.030 (0.530)	0.074 (0.122)
Cadmium (Cd, ug/dL)						–	0.319 (< .0001)	0.050 (0.294)	0.040 (0.407)
Cigarettes per day (CPD)							–	0.200 (< .0001)	0.006 (0.904)
Coffee intake (CI)								–	–0.089 (0.063)
Systolic blood pressure (SBP,mmHg)									–

* All cases matched to controls. The first group of control (n=183) were matched on age at randomization (±7 years), whole blood draw date (±20 days within the same season), pack-years of smoking (matched on either above or below the median of the ATBC cohort of 35 pack-years), ATBC treatment group, and time to follow-up (i.e.,controls having at least as much follow-up time as matched cases).The second group of controls (n=121) had been previously chosen for the Vitamin D Pooling Project (VDPP) and were matched on age at randomization (±1 year), whole blood draw date (±30 days within the same reason), assuring that the control is alive and cancer free at case diagnosis date.

Supplement Table 2 Crude and adjusted models for the risk of renal cell cancer with respect to coffee consumption among male smokers, Finland

Nested Case-Control	Coffee Consumption (cups/day)						P-trend
	Non-drinker	> 0 to < 1	≥ 1	≥ 2	≥ 3	≥ 4	
Total Participants	12	58	144	129	81	16	
Cases/Controls	4/8	14/44	43/101	44/85	25/56	6/10	
Crude HR (95%CI)	1.43 (0.39,5.32)	Reference	1.46 (0.72,2.95)	1.80 (0.84,3.68)	1.53 (0.71,3.32)	2.29 (0.68,7.69)	0.206
Model 1 HR* (95%CI)	1.19 (0.31,4.49)	Reference	1.43 (0.69,2.96)	1.95 (0.94,4.08)	1.49 (0.67,3.30)	2.59 (0.74,9.09)	0.516
Model 2 HR** (95%CI)	1.17 (0.72,3.12)	Reference	1.50 (0.72,3.12)	2.00 (0.95,4.21)	1.53 (0.68,3.45)	2.74 (0.77,3.45)	0.134

HR:hazard ratio; CI: confidence interval; 1 cup=278 grams

All cases matched to controls. The first group of control (n=183) were matched on age at randomization (± 7 years), whole blood draw date (± 20 days within the same season), pack-years of smoking (matched on either above or below the median of the ATBC cohort of 35 pack-years), ATBC treatment group, and time to follow-up (i.e., controls having at least as much follow-up time as matched cases). The second group of controls (n=121) had been previously chosen for the Vitamin D Pooling Project (VDPP) and were matched on age at randomization (± 1 year), whole blood draw date (± 30 days within the same reason), assuring that the control is alive and cancer free at case diagnosis date.

* Adjusted model includes groups of body mass index (underweight, normal, overweight and obese) and systolic blood pressure (normal, elevated, stage I and stage II).

** Adjusted model includes all variables in Model 1 as well as blood concentration of Cd, Hg and Pb. All cases matched to controls on age, whole blood draw date, pack-years of smoking, ATBC treatment group, and time to follow-up.