Coffee intake and trace element blood concentrations in association with renal cell cancer among smokers

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Abstract

Purpose 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. 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 Study. Cases diagnosed with RCC at 5 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 were more than threefold 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, is 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 [2–4]. 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 twofold increase in the prevalence of controlled hypertension in some countries [4]. Taken together, this suggests the need to identify additional factors for improved RCC prevention.

Coffee is estimated to contain more than a thousand chemicals, of which a small subset is known to be biologically active [5]. The elemental composition of coffee is geographically distinctive, and there is considerable variability in over 30 major (Ca, K, Mg, Na, S, P), minor (Cl, Co, Cr, Cu, Fe, Mn, Mo, Ni, Se, Sr, Zn), and trace (Al, As, B, Ba, Br, Cd, Hg, Pb, and Sn) elements, although estimated to contribute less than 10% of recommended dietary intakes (RDIs) for important nutritional elements (Ca, Cu, Cr, Fe, K, Mg, Mn, Ni, Sr, and Zn) [6]. Other bioactive components include polyphenols (e.g., flavonoids and chlorogenic acids), methylxanthines (caffeine, theophylline, and theobromine), diterpenes, nicotinic acid, and trigonelline [7]. Polyphenols are thought to play a role in the chemoprevention of cancer through antioxidant activity [8]. Coffee is the major dietary source of polyphenols, accounting for 40 to 45% of total daily intake in some populations [9, 10]. Notably, we and others have identified significantly reduced RCC risk...
associated with greater dietary intake of flavonoids (a subclass of polyphenols), including quercetin—also found in coffee beans [11, 12]. Caffeine and its metabolites have been shown to have pro-apoptotic and anti-inflammatory properties. Caffeine is known to induce apoptosis and reduce production of pro-inflammatory cytokines, like tumor necrosis factor (TNF)-α, IL-5, and IFN-γ [13]. In cervical cancer cell lines, theophylline and caffeine have been shown to synergistically enhance cell death [14].

Coffee may also act indirectly by reducing risk of other RCC risk factors. For example, a meta-analysis of observational studies suggests that high coffee intake is associated with a 30% reduction in the risk of diabetes [15]. 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 [15]. Contrary to a cardiovascular benefit, meta-analyses of randomized trials report 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 [15, 16]. 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) [17–19]. 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 [19–21]. Within high coffee intake regions, approximately 4% of dietary Pb intake has been attributed to coffee drinking [22]. 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) [23]. 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 [24, 25].

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 to 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 [26]. 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 6-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 a modified diet history, including both portion size and frequency of consumption. Dietary history of participants was collected by a Food Frequency Questionnaire in the Finnish language. Dietary consumption has been described elsewhere [27]. Briefly, participants were asked “how many cups of coffee and/or tea do you usually drink per day (or per week)?” Cup sizes were depicted in the questionnaire booklet as small, medium, and large. Participants were also asked about coffee additives, including table spoons of sugar, whipping cream, coffee cream, light cream, and milk. Approximately 2 to 5 years after completion of the baseline questionnaire (in 1990), participants were asked about usual coffee preparation methods including filtered (i.e., pouring water over ground, roasted coffee within a filter), boiled (i.e., pouring water on ground coffee and drinking when the grounds settle), instant, specialty (e.g., espresso), or a combination thereof with self-classification into one of eight mutually exclusive categories (filtered only, boiled only, instant only, specialty coffee (e.g., espresso), filtered and boiled, filtered and instant, boiled and instant, and no coffee).

Cumulative lifetime smoking exposure was estimated in pack-years, with one pack-year equal to 20 cigarettes smoked per day for 1 year. Because RCC has been associated with certain occupations, we included them in the analysis in order to investigate the possibility of confounding. High-risk occupations were defined as mining, colliery (coal mining), quarrying, stone masonry, stonemasonry, 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 [3].

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 [3]. 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) and 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-h fasting serum sample was collected at baseline from 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 [3].

**Trace element concentrations**

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

**Statistical analysis**

Quantitative variables were divided into quartiles based on the distribution among controls. The number of years from enrollment to cancer diagnosis was calculated as the number of days from enrollment to diagnosis divided by 365.25. Visually represented cup sizes (i.e., small, medium and large) from the questionnaire booklet were converted to the corresponding grams per day of coffee. In order to be consistent with prior research, we used the United States Department of Agriculture conversion table and defined one cup as 237 g of coffee (equivalent to one 8 fluid ounce cup).

Differences in categorical distributions were tested by the \( \chi^2 \) test, and in the event of a cell size less than five, the Fisher’s exact test was used. The Spearman’s (non-parametric) correlation coefficient was used to estimate the magnitude of the bivariate correlations between age, body mass index (BMI), coffee intake (g/day), cigarettes per day, systolic blood pressure, high-risk occupations, and whole blood concentrations of Cd, Hg, and Pb.

Crude and adjusted conditional logistic regression models were calculated using Proc PHREG in SAS. Adjusted models included factors known to be associated with RCC, including age, systolic blood pressure, and BMI. In the general population, whole blood Cd concentrations are most closely linked with tobacco use and smokers have approximately twofold greater blood concentrations compared with non-smokers (NHANES) [28]. In order to avoid over-adjustment for smoking using both cigarettes per day and whole blood Cd concentrations, we retained only whole blood Cd in all models in order to both test for the main effect of Cd and to test Cd as an adjustment variable. ATBC treatment group has been previously shown not to be associated with RCC and was therefore not included in this analysis [3]. Tests for trend were conducted by regressing the quartile median value, adjusting for other factors in the model. Two-way interactions were tested by multiplying the continuous value of each parameter together and testing the beta statistic for the interactive variable with the main effect terms in the adjusted conditional logistic regression model. Coffee intake and blood concentrations of trace elements were log transformed if used as continuous variables. Tests for additive effects between whole blood trace element concentrations and coffee intake were conducted by a categorical assessment of above/below median-combined categories (i.e., high coffee intake and high trace element intake and high coffee intake/and low trace element blood concentration). In order to maximize the number of individuals available for the stratified analysis of coffee preparation type, we defined filtered coffee use as individuals reporting filtered only and mixed (filtered plus boiled or filtered plus instant) coffee preparations. We defined boiled coffee use as individuals reporting boiled only and mixed (boiled plus filtered or boiled plus instant) coffee preparations. All statistical tests of significance (defined as \( p < 0.05 \)) were two-tailed. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

**Results**

The mean (±SD) total follow-up time was 16.3 years (12.1 ± 4.1 years (mean ± standard deviation) for cases and 18.1 ± 3.1 years for controls, data not shown). The mean age at baseline was 56.9 years, and mean number of cigarettes smoked per day was 20.1 (±8.1). Cases were significantly more likely than controls to have a history of hypertension \((p < 0.001)\) and elevated systolic blood pressure \((p < 0.007)\). There was no statistically significant difference in BMI or
matching variables (age and cigarettes per day, Table 1). At baseline, mean intake of coffee was 2.4 ± 1.4 cups/day (558 g/day ± 331 g/day) and 2.7% of study participants were non-coffee drinkers (data not shown). At follow-up, 76.8% of participants reported using any filter coffee, 18.4% used any boiled coffee, and 4.6% reported not drinking coffee (Supplemental Table 1). There was no difference in any filter coffee use between controls and cases (76.6 v. 77.2, \( p = 0.897 \), respectively). Any boiled coffee use was more frequent in controls than cases (20.4 v. 14.0%, respectively), although this difference was not statistically significant (\( p = 0.108 \)) (data not shown).

Among the risk factors we investigated, the greatest positive bivariate correlations were observed between number of cigarettes per day and whole blood Cd (\( \rho = 0.319, p < 0.001 \)) and cigarettes per day and coffee consumption (g/day) (\( \rho = 0.200, p < 0.001 \)); the greatest negative correlation observed was between cigarettes per day and age (\( \rho = -0.197, p < 0.001 \)) (Supplemental Table 1). Notably, correlations between coffee intake (g/day) and blood concentrations of Cd, Hg, and Pb were not statistically significant, with all \( \rho \) below 0.05 (Supplemental Table 3). Coffee intake was not significantly associated with RCC risk after adjusting for traditional RCC risk factors (Model 1, \( p\text{-trend} = 0.090 \)) nor after adjusting for traditional RCC risk factors plus blood concentrations of Cd, Hg, and Pb (Model 2, \( p\text{-trend}=0.094 \), Supplemental Table 3). Cigarettes per day and high-risk occupations were not significantly associated with RCC risk in either crude or adjusted models and therefore not included in the final model (data not shown). Although the study is matched on age and pack-years of smoking, we also tested these variables for an association with RCC due to the possibility of residual confounding but left them out of final models as they were not statistically significant. With respect to the main effects of trace elements (above vs. below median blood concentrations of Cd, Hg, and Pb), only Pb was significantly associated with RCC risk (HR=1.69, 95% CI 1.06, 2.85) (Table 2), as previously shown [3]. In additive tests of interaction, individuals with both above median coffee intake and above median blood Pb had a significantly greater risk of RCC, (HR=3.40, 95% CI 1.62, 7.13, \( p = 0.001 \)), compared to individuals having both below median (“low”) coffee intake (<2.3 cups/day) and below median whole blood Pb concentration (<3.20 ug/dL), Table 3. Adjusted HR values increased 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

### 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)      |                             |                         | 0.950          | 1.2      | 0.86, 1.55 | 0.328          |
| BMI (kg/m²)                      |                             |                         |                |          |            |                |
| 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 | 0.90, 3.12  |                |
| 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 using Pearson’s chi-squared test
* * * \( p \) values were calculated using Cox Proportional Hazards regression analysis

\( \rho \) correlation coefficient

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### 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 (≥ 0.94 ug/dL)              | 71/152          | 1.05 (0.70, 1.58)| 0.755   | 69/149          | 1.03 (0.59, 1.43)      | 0.096   |
| Lead (Pb)                        |                 |                  |         |                 |                        |         |
| Low (< 3.20 ug/dL)               | 51/143          | Reference        | 0.055   | 47/130          | Reference              | 0.026   |
| High (≥ 3.20 ug/dL)              | 85/161          | 1.55 (0.99, 2.41)| 0.055   | 81/160          | 1.69 (1.06, 2.85)      | 0.012   |
| Mercury (Hg)                     |                 |                  |         |                 |                        |         |
| Low (< 2.70 ug/dL)               | 74/151          | Reference        | 0.229   | 68/142          | Reference              | 0.141   |
| High (≥ 2.70 ug/dL)              | 62/153          | 0.78 (0.52, 1.17)| 0.755   | 60/148          | 0.73 (0.48, 1.11)      | 0.380   |

** HR hazard ratio, CI confidence interval

*p-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) was 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 was matched on age at randomization (±1 year) and 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 2.3 cups (< 550 g/day) and below median Pb (<3.20 ug/dL)  | Reference    |          |         |
| ≥ 2.3 cups (≥ 550 g/day) and below median Pb (<3.20 ug/dL)          | 2.68         | 1.26, 5.71| 0.011   |
| Less than 2.3 cups (< 550 g/day) and above median Pb (≥3.20 ug/dL)  | 2.67         | 1.26, 5.65| 0.010   |
| ≥ 2.3 cups (≥ 550 g/day) and above median Pb (≥3.20 ug/dL)          | 3.40         | 1.62, 7.13| 0.001   |
| P-trend**                                                          |              |          |         |
| **Cadmium (Cd)**                                                   |              |          |         |
| Less than 2.3 cups (< 550 g/day) and below median Cd (<0.94 ug/dL)  | Reference    |          |         |
| ≥ 2.3 cups (≥ 550 g/day) and below median Cd (<0.94 ug/dL)          | 1.85         | 0.94, 3.65| 0.076   |
| Less than 2.3 cups (< 550 g/day) and above median Pb (≥0.94 ug/dL)  | 1.12         | 0.54, 2.32| 0.757   |
| ≥ 2.3 cups (≥ 550 g/day) and above median Pb (≥0.94 ug/dL)          | 1.71         | 0.90, 3.25| 0.102   |
| P-trend**                                                          |              |          |         |
| **Mercury (Hg)**                                                   |              |          |         |
| Less than 2.3 cups (< 550 g/day) and below median Hg (<2.70 ug/dL)  | Reference    |          |         |
| ≥ 2.3 cups (≥ 550 g/day) and below median Hg (<2.70 ug/dL)          | 2.00         | 1.06, 3.77| 0.032   |
| Less than 2.3 cups (< 550 g/day) and above median Pb (≥2.70 ug/dL)  | 0.91         | 0.46, 1.80| 0.786   |
| ≥ 2.3 cups (≥ 550 g/day) and above median Pb (≥2.70 ug/dL)          | 1.24         | 0.65, 2.34| 0.517   |
| P-trend**                                                          |              |          |         |

** 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 controls (n=183) was 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 was matched on age at randomization (±1 year) and 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) of the comparison groups as ordered in the table.
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 (<2.3 cups/day) and below median whole Hg concentration (2.70 ug/dL). There were no significant associations with RCC risk for any combination of coffee intake and blood Cd (Table 3). When the additive interaction models were stratified by any filtered coffee use, we found that, in general, risk estimates increased. For example, the HR for above median Pb and above median coffee intake (v. below median Pb and below median coffee intake) increased slightly (HR = 3.90, 95% CI 1.60, 9.49, p-trend = 0.003 (Supplemental Table 4). The stratified model for boiled coffee use did not converge as there were too few individuals in this category.

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 (>2.3 cups per day) and higher blood Pb concentrations (>3.20 ug/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; 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 [29, 30].

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 [31–35]. 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 [23, 36, 37]. 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 [38]. 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 are not known [39–41]. 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 [42, 43]. Multiple germline VHL mutations are associated with multiple family cancer syndromes which include RCC as a prominent feature [44]. 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) [45, 46]. In contrast, compounds in coffee (i.e., flavanones) reduce tumor formation via the VHL pathway [47]. Phenolic acids and diterpenes found in coffee have been reported as potent inhibitors of cancer proliferation via the induction of apoptosis [8, 47, 48]. Notably, diterpene concentrations are substantially influenced by type of coffee preparation method. For example, the concentration of total kahweol esters has been shown to be 5,000-fold greater in boiled (unfiltered) versus filtered coffee [49]. Our risk estimates of the combined exposure of coffee and heavy metals (Cd, Hg, and Pb) on RCC risk were slightly increased when focused on filter coffee users alone. Future studies should collect detailed information on coffee preparation methods. 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 [50]. At least one cohort study of acrylamide intake has reported elevated RCC risk in humans, although not in another study [51, 52]. Coffee is one of the top three dietary contributors to total acrylamide intake in the general population [52]. 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 [50]. 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 [23]. According to trade statistics, the average per capita consumption of roasted coffee relevant to the time period of this cohort in Finland was 10.1 kg per year in 1989 [53]. Limitations of this study include the absence of information on the constituents in coffee consumed (e.g., trace elements), coffee type (e.g., decaffeinated), coffee roast (light v. dark), and storage duration. Compared with stored coffee, polyphenol content of freshly
roasted coffee differs by as much as tenfold [54]. Coffee roasting methods can alter acrylamide production. The highest acrylamide concentrations are found in light roasts, which may be as much as twofold greater than dark roasts and at times exceeding the 2017 European Commission 400 µg/kg benchmark level [55]. We also had no information on RCC histologic subtype which has at least nine molecular and three histologic subtypes [56]. 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-butane (NNK) [46, 57]. 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 (ρ = 0.40) in a rural population [58]. Future studies are needed that account for the mutational profile of the tumors that are known to influence these biologic pathways.

**Conclusion**

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

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10552-021-01505-2.

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

**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study did not include personal identifiers and was classified as non-Human research by the Pennsylvania State University IRB.

**Consent to participate** All participants provided written informed consent at the time of cohort enrollment.

**Consent to publication** This study has been reviewed by the Division of Cancer Epidemiology and Genetics at the National Cancer Institute.

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