



## Original article

## Coffee and tea drinking and risk of cancer of the urinary tract in male smokers



Maryam Hashemian, MD, PhD<sup>a, b, \*</sup>, Rashmi Sinha, PhD<sup>a</sup>, Gwen Murphy, PhD, MPH<sup>a</sup>, Stephanie J. Weinstein, PhD<sup>a</sup>, Linda M. Liao, PhD<sup>a</sup>, Neal D. Freedman, PhD, MPH<sup>a</sup>, Christian C. Abnet, PhD, MPH<sup>a</sup>, Demetrius Albanes, MD<sup>a</sup>, Erikka Loftfield, PhD<sup>a</sup>

<sup>a</sup> Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD

<sup>b</sup> Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

## ARTICLE INFO

## Article history:

Received 8 November 2018

Accepted 30 March 2019

Available online 3 April 2019

## Keywords:

Coffee

Tea

Bladder cancer

Renal cell carcinoma

Caffeine

Catechin

## ABSTRACT

**Purpose:** We evaluated the association of coffee and tea drinking with risk of the urinary tract cancer in Finnish men, with high coffee consumption, using data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.

**Methods:** The ATBC trial conducted from 1985 to 1993 enrolled 29,133 male smokers. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and confidence intervals (CIs), using men who drank more than 0 but less than 1 cup coffee/d and tea nondrinkers as our referent group for coffee and tea analyses, respectively.

**Results:** During 472,402 person-years of follow-up, 835 incident cases of bladder cancer and 366 cases of renal cell carcinoma were ascertained. For bladder cancer, we observed no association for coffee consumption (HR  $\geq 4$  vs.  $>0$  to  $<1$  cups/d = 1.16, 95% CI = 0.86–1.56) and a borderline statistically significant inverse association for tea consumption (HR  $\geq 1$  vs. 0 cup/d = 0.77, 95% CI = 0.58–1.00). For renal cell carcinoma, we observed no association for coffee (HR  $\geq 4$  vs.  $>0$  to  $<1$  cups/d = 0.85, 95% CI = 0.55–1.32) or tea consumption (HR  $\geq 1$  vs. 0 cup/d = 1.00, 95% CI = 0.68–1.46). We found no impact of coffee preparation on coffee-cancer associations.

**Conclusions:** Coffee drinking was not associated with urinary tract cancers risk. Further research on tea and bladder cancer is warranted.

Published by Elsevier Inc.

## Introduction

After water, coffee and tea are the two most commonly consumed drinks worldwide. Coffee drinking has been consistently and inversely associated with liver [1] and endometrial cancer [2]. A pooled analysis including 13 prospective cohort studies found suggestive inverse associations between coffee drinking and renal cell carcinoma (RCC) [3], but adverse associations between coffee drinking and risk of bladder cancer in case-control studies [4] have raised concerns that coffee consumption could be harmful. A meta-analysis including 34 case-control studies and six prospective

cohort studies observed a positive association between coffee drinking and bladder cancer, particularly among men [4], but another meta-analysis found no evidence of a coffee-bladder cancer association [5]. Results have also been inconsistent for smokers versus nonsmokers with some studies only reporting a positive association between coffee and bladder cancer among nonsmokers [5] and others only reporting a positive association among smokers [6]. Smoking is a known risk factor for bladder cancer, and incidence rates in men are highest in Europe and North America, with global trends reflecting the prevalence of tobacco smoking [7].

Coffee contains many phenolic compounds and diterpenes, such as cafestol and kahweol, which may reduce the genotoxicity of some carcinogens [8]. Unfiltered coffees, including boiled coffee, contain relatively high levels of cafestol and kahweol but low or negligible levels are found in instant or filtered coffees [9]. Few studies collect data on coffee preparation method, and no prospective studies have evaluated the impact of preparation method on the association of coffee drinking with cancer of the urinary

Conflict of interest: None declared.

\* Corresponding author. Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD. Tel.: +1 240 276 7873; fax: +1 240 276 7378.

E-mail address: hashemian3@gmail.com (M. Hashemian).

<https://doi.org/10.1016/j.annepidem.2019.03.014>

1047-2797/Published by Elsevier Inc.

tract. A meta-analysis highlighted the need for prospective studies investigating the impact of coffee preparation method [5].

Tea drinking has been inversely associated with certain types of cancer including oral cancer [10], and tea contains polyphenols such as catechins with antioxidant properties [11] that have been shown to prevent tumor progression by interfering in cell signaling in experimental studies [11]. However, epidemiologic studies of tea drinking and cancer of the urinary tract have yielded inconsistent results [3,12], and few studies have considered the association among smokers. A pooled analysis including 13 prospective cohort studies found suggestive inverse associations between tea drinking and RCC [3], and a report by the World Cancer Research Fund and the American Institute for Cancer Research concluded that there is limited suggestive evidence of an inverse association between tea and bladder cancer [13].

Per capita consumption of coffee in Finland is among the highest in the world [14], and both tobacco smoking and male sex are major risk factors for bladder cancer [7]. Thus, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (ATBC), a cohort of Finnish male smokers with a high prevalence of heavy coffee drinking who also provided information on coffee preparation method and tea drinking, provided a unique opportunity to study the association of coffee and tea drinking with bladder cancer and RCC.

## Materials and methods

### Study design

The ATBC Trial, which investigated whether vitamin supplementation could prevent lung cancer in smokers, was conducted in Finland from 1985 to 1993 and enrolled 29,133 male smokers. The design of the ATBC Trial and subsequent cohort study have been described elsewhere [15]. In brief, male smokers were eligible to participate if they smoked at least five cigarettes/d, had no history of cancer or a serious disease limiting long-term follow-up, and were not using vitamin supplements at date of randomization. Eligible men who gave informed consent were randomized to one of four groups using a 2\*2 factorial design: Beta Carotene (20 mg/d) and/or Alpha Tocopherol (50 mg/d). The trial ended in April 1993; however, follow-up continued for cancer incidence and death using the Finnish Cancer Registry and the Registry of Cause of Death, respectively, providing complete ascertainment of cases [16]. The study protocol was approved by the Institutional Review Board of the National Cancer Institute in the United States and the National Institute for Health and Welfare in Finland [15].

For our analysis, we excluded men with a self-reported history of renal failure ( $n = 57$ ), as this condition may alter fluid consumption, those with extreme energy intake, defined as more than two interquartile ranges above the 75th percentile or below the 25th percentile of energy intake ( $n = 213$ ) and those missing data on coffee or tea consumption ( $n = 2022$ ). Our final analytic sample included 26,841 men.

### Outcome ascertainment

Incident cancer cases were ascertained via the Finnish Cancer Registry and medical records [17,18]. Bladder cancers were defined as ICD-9 code 188 or 233.7 and RCC as ICD-9 code 189.0. Renal pelvis/ureter cancers (ICD-9 code 189.1 and 189.2) were not included in our case definition due to small sample size ( $n = 62$ ). Follow-up time (i.e., person-years) was calculated from date of randomization (i.e. baseline assessment) to date of death, date of bladder cancer or RCC diagnosis, or end of follow-up (i.e., December 31, 2015), whichever came first. Because bladder cancer and RCC

have different risk factors, most notably tobacco smoking, we analyzed these outcomes separately.

### Exposure assessment

A validated 276-item food frequency questionnaire (FFQ), which included foods commonly consumed in Finland, and picture book illustrating portion sizes were used to collect information about usual dietary intake during the previous year [19]. Coffee and tea consumptions were assessed separately as cups per day or per week. Cup size was ascertained using pictures depicting common portion sizes. Data on frequency and portion size were used to estimate the number of grams of coffee and tea typically consumed per day with typical cup sizes ranging from 70 to 170 grams for coffee and 110–220 grams for tea. We converted grams to cups using USDA conversion tables, estimating that 237 grams of coffee or tea equals one 8-fluid ounce cup [20], to enable comparison with prior research on coffee and cancer [6,20]. A study conducted to evaluate the reproducibility and validity of the ATBC dietary assessment very high intraclass correlation coefficients for coffee consumption (ranging from 0.72 to 0.79), comparing data from food records and FFQs [19]. In 1990, approximately two to five years after baseline, participants reported how they usually prepared their coffee using four predefined categories: 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, or a combination of the methods, and no coffee drinking. In total, 20,603 men provided data on coffee preparation. Approximately 71% and 21% of the participants reported usually drinking filtered and boiled coffee, respectively. Type of tea was not specified in the questionnaire as black tea was the predominant type of tea consumed in Finland at the time of the study.

Demographic data, past medical history, and smoking status were obtained at the time of randomization. Body mass index (BMI) was computed from measured height and weight ( $\text{kg}/\text{m}^2$ ). Hypertension was defined as blood pressure readings at baseline of systolic blood pressure more than 140 mm Hg and/or diastolic blood pressure more than 90 mm Hg, or self-reported history of hypertension. The baseline questionnaire queried occupational exposure to lead refining, nickel refining, copper smelting, steel production, oil refining, gas manufacture, manufacture of chromium pigments, arsenic production, or foundry work. We adjusted for these potential bladder cancer-related occupational exposures [21], using dummy variables in our multivariable adjusted models.

### Statistical analysis

Coffee drinkers were categorized into one of six groups (nondrinkers,  $>0$  but  $<1$ ,  $\geq 1$ ,  $\geq 2$ ,  $\geq 3$ , or  $\geq 4$  cups/d), and tea drinkers were categorized into one of three groups (nondrinkers,  $<1$ , or  $\geq 1$  cup/d). Coffee drinkers who reported consuming more than zero but less than one cup of coffee per day were used as the referent group for coffee analyses because few men in this cohort were coffee nondrinkers. However, there were a considerable number of tea nondrinkers; thus, analyses of tea consumption use tea nondrinkers as the referent group. For continuous analyses, we estimated the hazard ratios (HRs) associated with a one cup per day increase in either coffee or tea consumption.

Multivariable Cox proportional hazards regression models were used to estimate HRs and 95% confidence intervals (CIs) for categories of coffee or tea consumption and cancers of the urinary tract. Linear trends across categories were evaluated using the median consumption of each category. We used person-years as the underlying time metric. Using age as the underlying metric yielded similar results (data not shown).

**Table 1**  
Baseline characteristics of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study by coffee and tea consumption ( $n = 26,841$ )

| Characteristic  | Coffee consumption (cups/d) <sup>*</sup> |               |               |               |               |               | <i>P</i> | Tea consumption (cups/d) <sup>*</sup> |               |               |          |
|---|--|---------------|---------------|---------------|---------------|---------------|----------|---------------------------------------|---------------|---------------|----------|
|   | Nondrinkers                              | <1            | ≥1            | ≥2            | ≥3            | ≥4            |          | Nondrinker                            | <1            | ≥1            | <i>P</i> |
| No. of participants   | 670                                      | 3086          | 7175          | 8042          | 4472          | 3396          |          | 17204                                 | 7266          | 2371          |          |
| Randomization group,%   |  |               |               |               |               |               | .26      |                                       |               |               | .33      |
| Placebo   | 29.0                                     | 24.8          | 25.1          | 24.9          | 24.8          | 25.6          |          | 24.8                                  | 25.7          | 25.5          |          |
| AT <sup>†</sup>   | 21.3                                     | 25.2          | 25.6          | 24.1          | 25.3          | 25.5          |          | 25.2                                  | 24.0          | 25.7          |          |
| BC <sup>‡</sup>   | 23.7                                     | 25.3          | 24.6          | 25.2          | 25.2          | 25.1          |          | 25.0                                  | 25.4          | 24.2          |          |
| AT + BC   | 26.0                                     | 24.7          | 24.7          | 25.8          | 24.8          | 23.8          |          | 25.0                                  | 24.9          | 24.6          |          |
| Age, y <sup>§</sup>   | 57.2 ± 5.0                               | 57.6 ± 5.0    | 57.8 ± 5.2    | 57.3 ± 5.1    | 56.5 ± 4.8    | 56.2 ± 4.7    | <.0001   | 57.2 ± 5.0                            | 57.2 ± 5.1    | 57.1 ± 5.1    | .73      |
| BMI <sup>§</sup> , kg/m <sup>2</sup>                            | 25.9 ± 4.2                               | 26.4 ± 3.8    | 26.3 ± 3.8    | 26.2 ± 3.7    | 26.3 ± 3.7    | 26.4 ± 3.8    | .01      | 26.3 ± 3.8                            | 26.2 ± 3.7    | 26.2 ± 3.7    | .52      |
| Years of smoking <sup>§</sup>                                   | 36.1 ± 8.2                               | 35.7 ± 9.0    | 36.2 ± 8.6    | 35.8 ± 8.5    | 35.7 ± 7.9    | 36.1 ± 7.9    | .001     | 36.2 ± 8.3                            | 35.4 ± 8.6    | 35.4 ± 8.6    | <.0001   |
| No. of cigarette/d <sup>§</sup>                                 | 20.7 ± 9.8                               | 19.2 ± 9.0    | 19.0 ± 8.2    | 20.1 ± 8.5    | 21.5 ± 8.7    | 23.5 ± 9.4    | <.0001   | 20.8 ± 8.3                            | 19.7 ± 8.6    | 19.4 ± 8.9    | .06      |
| Alcohol <sup>§</sup> , g/d                                      | 23.6 ± 26.6                              | 26.7 ± 28.1   | 19.7 ± 21.8   | 15.9 ± 18.8   | 15.1 ± 18.4   | 13.5 ± 18.4   | <.0001   | 17.4 ± 21.1                           | 18.9 ± 21.7   | 18.7 ± 22.5   | <.0001   |
| Education, greater than high school, %                          | 64.5                                     | 72.1          | 70.6          | 65.6          | 64.4          | 59.0          | <.0001   | 62.5                                  | 74.6          | 71.9          | <.0001   |
| History of diabetes, %  | 5.1                                      | 5.1           | 4.2           | 3.8           | 4.3           | 4.3           | .05      | 4.4                                   | 4.0           | 3.7           | .12      |
| Physical activity in leisure time, < 1/wk (the lowest category) | 53.3                                     | 51.1          | 47.2          | 51.0          | 55.3          | 57.7          | <.0001   | 53.4                                  | 48.1          | 49.1          | <.0001   |
| Family history of bladder cancer, %                             | 1.1                                      | 1.2           | 1.1           | 1.2           | 1.3           | 1.4           | .91      | 1.2                                   | 1.1           | 1.6           | .38      |
| Tea drinker   | 61.2                                     | 60.4          | 42.9          | 31.5          | 25.4          | 18.4          | <.0001   |                                       |               |               |          |
| Coffee drinker  |  |               |               |               |               |               |          | 98.5                                  | 98.1          | 88.7          | <.0001   |
| Energy <sup>§</sup> , kcal/d                                    | 2526 ± 724                               | 2475 ± 688    | 2534 ± 671    | 2669 ± 672    | 2815 ± 704    | 2942 ± 776    | <.0001   | 2643 ± 711                            | 2701 ± 704    | 2724 ± 717    | <.0001   |
| Fruit consumption <sup>§</sup> , grams/d                        | 88.0 ± 84.0                              | 97.2 ± 82.9   | 97.6 ± 81.0   | 93.2 ± 80.7   | 89.1 ± 83.4   | 85.3 ± 88.1   | <.0001   | 88.5 ± 82.6                           | 101.8 ± 81.5  | 99.0 ± 83.9   | <.0001   |
| Vegetable consumption <sup>§</sup> , grams/d                    | 274.9 ± 274.9                            | 282.8 ± 101.6 | 296.1 ± 100.8 | 294.3 ± 101.9 | 293.8 ± 105.8 | 287.4 ± 110.7 | <.0001   | 287.6 ± 102.9                         | 302.6 ± 104.1 | 291.6 ± 105.0 | <.0001   |
| Presence of hypertension, %                                     | 23.6                                     | 25.4          | 21.4          | 17.7          | 16.4          | 13.7          | <.0001   | 18.8                                  | 19.0          | 20.8          | <.0001   |

\* One 8-oz cup = 237 grams of coffee or tea.

† Alpha-Tocopherol.

‡ Beta-Carotene.

§ Mean ± SD.

**Table 2**  
Hazard ratios (95% confidence intervals) for cancer of urinary system according to coffee consumption in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

| Model adjustment                      | Coffee consumption (cups/d) <sup>*</sup> |           |                  |                  |                  |                  | P trend | 1 cup/d increase |
|---------------------------------------|--|-----------|------------------|------------------|------------------|------------------|---------|------------------|
|                                       | Nondrinker                               | <1        | ≥1               | ≥2               | ≥3               | ≥4               |         |                  |
| <b>Bladder cancer</b>                 |  |           |                  |                  |                  |                  |         |                  |
| No of cases/person-years              | 17/10,452                                | 80/51,228 | 214/124,128      | 256/143,952      | 149/81,838       | 119/61,468       |         |                  |
| Unadjusted model                      | 1.06 (0.63–1.79)                         | 1         | 1.09 (0.84–1.41) | 1.12 (0.64–1.75) | 1.13 (0.86–1.48) | 1.20 (0.91–1.60) | .21     | 1.03 (0.99–1.08) |
| Multivariable adjusted <sup>†</sup>   | 1.03 (0.61–1.74)                         | 1         | 1.04 (0.81–1.35) | 1.06 (0.82–1.37) | 1.10 (0.83–1.46) | 1.16 (0.86–1.56) | .29     | 1.03 (0.98–1.08) |
| Multivariable adjusted <sup>‡</sup>   | 1.03 (0.61–1.74)                         | 1         | 1.02 (0.79–1.32) | 1.02 (0.79–1.32) | 1.05 (0.79–1.40) | 1.10 (0.81–1.49) | .52     | 1.02 (0.97–1.07) |
| <b>Renal cell carcinoma</b>           |  |           |                  |                  |                  |                  |         |                  |
| No of cases/person-years              | 9/10,720                                 | 42/52,462 | 92/121,975       | 113/144,756      | 65/80,496        | 45/61,128        |         |                  |
| Unadjusted model                      | 1.05 (0.51–2.16)                         | 1         | 0.90 (0.62–1.29) | 0.95 (0.67–1.35) | 0.95 (0.64–1.40) | 0.88 (0.58–1.34) | .69     | 0.99 (0.92–1.06) |
| Multivariable adjusted <sup>†,§</sup> | 1.03 (0.50–2.12)                         | 1         | 0.86 (0.60–1.25) | 0.92 (0.64–1.32) | 0.94 (0.63–1.40) | 0.85 (0.55–1.32) | .68     | 0.99 (0.92–1.07) |
| Multivariable adjusted <sup>‡,§</sup> | 1.03 (0.50–2.12)                         | 1         | 0.87 (0.60–1.27) | 0.94 (0.65–1.36) | 0.96 (0.64–1.45) | 0.88 (0.56–1.38) | .82     | 0.99 (0.92–1.08) |

\* One 8-oz cup = 237 grams of coffee.

† Adjusted for age (continuous), BMI (kg/m<sup>2</sup>, continuous), level of education (high school or less, greater than high school), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (grams/d, continuous), history of diabetes (yes or no), frequency of physical activity in leisure time (<1/wk, 1–2/wk, ≥3/wk), energy (kcal/d, continuous), nutrient density-adjusted fruit consumption (grams/d, continuous), nutrient density-adjusted vegetable consumption (grams/d, continuous).

‡ Additionally adjusted for tea consumption (drinker, nondrinker).

§ Additionally adjusted for presence of hypertension.

We adjusted multivariable models for potential confounders including: age (years), BMI (kg/m<sup>2</sup>), level of education/training (less than or equal to a high school education or more than a high school education), smoking duration (years), smoking intensity (cigarettes per day), alcohol (grams/d), history of diabetes (yes or no), frequency of physical activity in leisure time (<1/wk, 1–2/wk, or ≥3/wk), energy intake (kcal/d), nutrient density-adjusted fruit consumption (grams/d), and nutrient density-adjusted vegetable consumption (grams/d). For RCC analyses, we additionally adjusted for the presence of hypertension. We also mutually adjusted for coffee and tea consumption in tea and coffee models, respectively.

In secondary analyses of coffee drinking and cancers, we collapsed the two highest coffee consumption categories to preserve sample size. We tested for potential effect modification by smoking status and method of preparation by comparing models with and without the interaction term between coffee or tea consumption (continuous) and continuous pack-years or each level of coffee preparation method using the likelihood ratio test. To evaluate the impact of smoking on risk estimates, we stratified by median pack-years. Next, to explore the impact of coffee preparation method, we adjusted for consumption of filtered, boiled, instant, or a combination of coffee types using categorical variables in a subset of participants ( $n = 20,603$ ) with information on method of preparation. We compared the HRs from the multivariable adjusted model to the model additionally adjusted for preparation

method, using likelihood ratio test. We also stratified by method of coffee preparation defined as either filtered or boiled (the most common methods). Finally, to evaluate potential reverse causality, we excluded participants with less than two years of follow-up. We observed no deviations from the proportional hazards assumption using the Schoenfeld residuals test ( $P = .24$  for coffee;  $P = .16$  for tea consumption).

$P$  values of less than 0.05 were considered statistically significant, and all tests were two-sided. All statistical analyses were carried out using STATA software (version 14, STATA Corp, College Station, TX).

## Results

During 472,402 person-years of follow-up, 835 incident cases of bladder cancer and 366 incident cases of RCC were ascertained. Median follow-up time was 17.6 years, and mean age at baseline was 57.2 years. Approximately 98% of participants reported drinking coffee and 36% reported drinking tea at baseline. Mean consumption among drinkers was 2.3 cups/d for coffee and 0.7 cups/d for tea. The mean ( $\pm$ SD) number of cigarettes smoked per day was 20.4 ( $\pm$ 8.8), and the mean number of years smoked was 35.9 ( $\pm$ 8.4). Participants who reported heavier coffee drinking tended to be younger, smoke more cigarettes per day, drink less alcohol and less tea, be less educated, have a lower prevalence of hypertension, and

**Table 3**  
Hazard ratios (95% confidence intervals) for cancer of urinary system according to tea consumption in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

| Model adjustment                    | Tea consumption (cups/d) <sup>*</sup> |                  |                  | P trend | 1 cup/d increase |
|-------------------------------------|---------------------------------------|------------------|------------------|---------|------------------|
|                                     | Nondrinker                            | <1               | ≥1               |         |                  |
| <b>Bladder cancer</b>               |                                       |                  |                  |         |                  |
| No. of cases/person-years           | 553/297,629                           | 223/132,968      | 59/42,441        |         |                  |
| Unadjusted model                    | 1                                     | 0.88 (0.76–1.03) | 0.73 (0.56–0.96) | .02     | 0.90 (0.80–1.01) |
| Multivariable adjusted <sup>†</sup> | 1                                     | 0.91 (0.78–1.07) | 0.77 (0.58–1.00) | .046    | 0.92 (0.82–1.03) |
| Multivariable adjusted <sup>‡</sup> | 1                                     | 0.92 (0.78–1.08) | 0.77 (0.58–1.02) | .07     | 0.92 (0.82–1.04) |
| <b>Renal cell carcinoma</b>         |                                       |                  |                  |         |                  |
| No. of cases/person-years           | 226/292,468                           | 109/130,788      | 31/42,678        |         |                  |
| Unadjusted model                    | 1                                     | 1.07 (0.85–1.35) | 0.96 (0.66–1.39) | .86     | 0.99 (0.85–1.15) |
| Multivariable adjusted <sup>†</sup> | 1                                     | 1.11 (0.88–1.40) | 1.00 (0.68–1.46) | .95     | 1.01 (0.86–1.17) |
| Multivariable adjusted <sup>‡</sup> | 1                                     | 1.10 (0.87–1.40) | 0.97 (0.65–1.44) | .92     | 0.99 (0.84–1.16) |

\* One 8-oz cup = 237 grams of tea.

† Adjusted for age (continuous), BMI (kg/m<sup>2</sup>, continuous), level of education (high school or less, greater than high school), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (grams/d, continuous), tea consumption (drinker, nondrinker), history of diabetes (yes or no), frequency of physical activity in leisure time (<1/wk, 1–2/wk, ≥3/wk), energy (kcal/d, continuous), nutrient density-adjusted fruit consumption (grams/d, continuous), nutrient density-adjusted vegetable consumption (grams/d, continuous).

‡ Additionally adjusted for coffee consumption (cups/d).

**Table 4**  
Hazard ratios (95% confidence intervals) for bladder cancer according to coffee consumption in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study stratified by smoking status (n = 26,841)

| Model adjustment        | Coffee (cups/d)* |    |                  |                  | Tea (cups/d)*    |                  |                  |    | P trend | P interaction | P trend | P interaction |
|-------------------------|------------------|----|------------------|------------------|------------------|------------------|------------------|----|---------|---------------|---------|---------------|
|                         | <1               | ≥1 | ≥2               | ≥3               | Nondrinker       | <1               | ≥1               | ≥2 |         |               |         |               |
| ≤35 pack-years          |                  |    |                  |                  |                  |                  |                  |    |         |               |         |               |
| No of cases             | 9                | 34 | 115              | 107              | 249              | 109              | 32               |    |         |               |         | .73           |
| Multivariable adjusted† | 1.45 (0.69–3.02) | 1  | 1.33 (0.91–1.96) | 1.36 (0.92–2.00) | 1.44 (0.97–2.15) | 0.85 (0.68–1.07) | 0.79 (0.55–1.15) |    |         |               |         | .19           |
| >35 pack-years          |                  |    |                  |                  |                  |                  |                  |    |         |               |         |               |
| No of cases             | 8                | 46 | 99               | 161              | 304              | 114              | 27               |    |         |               |         |               |
| Multivariable adjusted† | 0.75 (0.35–1.59) | 1  | 0.82 (0.28–1.17) | 0.83 (0.29–1.17) | 0.90 (0.53–1.26) | 0.96 (0.77–1.20) | 0.73 (0.49–1.09) |    |         |               |         | .13           |

\* One 8-oz cup = 237 grams of coffee or tea.

† Adjusted for age (continuous), BMI (kg/m<sup>2</sup>, continuous), level of education (high school or less, greater than high school), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (grams/d, continuous), tea consumption (drinker, nondrinker), history of diabetes (yes or no), frequency of physical activity in leisure time (<1/wk, 1–2/wk, ≥3/wk), energy (kcal/d, continuous), nutrient density-adjusted fruit consumption (grams/d, continuous), nutrient density-adjusted vegetable consumption (grams/d, continuous).

consume more calories and vegetables but less fruit per day (Table 1). Participants who reported heavier tea drinking tended to smoke for fewer years, be more educated, drink less coffee, have a higher prevalence of hypertension, and consume more calories, fruits, and vegetables per day (Table 1).

We observed no statistically significant associations for coffee drinking (HR ≥4 vs. >0 to <1 cups/d = 1.16, 95% CI = 0.86–1.56, P trend = .29, Table 2) and a nonsignificant inverse association for tea drinking (HR ≥1 vs. 0 cup/d = 0.77, 95% CI = 0.58–1.00, P trend = .05, Table 3) with bladder cancer in multivariable adjusted models. In analyses of continuous coffee and tea consumption, we observed no statistically significant associations between either coffee (HR1 cup/d increase = 1.03; 95% CI 0.98–1.08) or tea (HR1 cup/d increase = 0.92; 95% CI 0.82–1.03) consumption and bladder cancer.

In multivariable adjusted models, we observed no statistically significant associations for either coffee drinking (HR ≥4 vs. >0 to <1 cups/d = 0.85, 95% CI = 0.55–1.32, P trend = .68, Table 2) or tea drinking (HR ≥1 vs. 0 cup/d = 1.00, 95% CI = 0.68–1.46, P trend = .95, Table 3) with RCC in multivariable adjusted models. In analyses of continuous coffee and tea consumption, we observed no statistically significant associations between either coffee (HR1 cup/d increase = 0.99; 95% CI 0.92–1.07) or tea (HR1 cup/d increase = 1.01; 95% CI 0.86–1.17) consumption and RCC risk. Additional adjustment for occupation or randomization group did not substantially alter risk estimates in analyses of coffee or tea (data not shown).

Smoking status, defined using pack-years, did not modify coffee- or tea-bladder cancer associations (P interaction = .66 and .73, respectively, Table 4).

Next, we considered the impact of coffee preparation method on the association between coffee and cancers of the urinary tract (Table 5). Among 20,603 men with information on preparation method, 71% drank filtered coffee, 21% drank boiled coffee, and 8% drank instant coffee or were not coffee drinkers. Baseline characteristics of the subset of men with data on preparation method were similar to the overall cohort [20]. Overall, adjustment for coffee preparation method did not alter the risk estimates for bladder cancer significantly (P for likelihood ratio test = .71). We found no statistical evidence of effect modification by preparation method (P interaction = .15) (Table 5). For the RCC analysis, adjustment for coffee preparation method substantially altered risk estimates (i.e., >10% change in HR estimates). However, we found no statistical evidence of effect modification by preparation method for RCC analysis (P interaction = .66; Table 5). Finally, restricting the analysis to those who were followed for at least two years did not meaningfully alter HR estimates (data not shown).

**Discussion**

In this prospective cohort study of male Finnish smokers, we found no evidence of an association between coffee consumption and bladder cancer risk, and method of preparation did not appear to modify estimates. We observed an inverse association between tea and bladder cancer risk that approached statistical significance but found no evidence of an association for coffee or tea drinking with RCC risk.

For bladder cancer, our results are consistent with other prospective studies such as the Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO) Study and the NIH-AARP Study, which found no association between coffee drinking and risk of bladder cancer following careful adjustment for potential confounders, particularly cigarette smoking [6,22]. However, our results are not consistent with the results of two Japanese cohorts, which observed an inverse association between coffee drinking and bladder cancer [23]. Coffee drinkers in the Japanese cohorts were more highly educated, were more likely to be employed, and had

**Table 5**  
Hazard ratios (95% confidence intervals) for cancer of urinary system according to coffee consumption in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study among those with information on coffee preparation method ( $n = 20,603$ )

| Model adjustment                    | Coffee (cups/d) <sup>*</sup> |                  |                  |                  | P trend | P interaction |
|-------------------------------------|------------------------------|------------------|------------------|------------------|---------|---------------|
|                                     | <1                           | ≥1               | ≥2               | ≥3               |         |               |
| <b>Bladder cancer</b>               |                              |                  |                  |                  |         |               |
| All methods of preparing coffee     |                              |                  |                  |                  |         | .15           |
| No of cases                         | 67                           | 174              | 215              | 229              |         |               |
| Multivariable adjusted <sup>†</sup> | 1                            | 0.99 (0.74–1.31) | 1.02 (0.78–1.36) | 1.11 (0.84–1.48) | .18     |               |
| Multivariable adjusted <sup>‡</sup> | 1                            | 0.98 (0.73–1.30) | 1.01 (0.77–1.34) | 1.10 (0.83–1.47) | .31     |               |
| Filtered method of preparing coffee |                              |                  |                  |                  |         |               |
| No of cases                         | 51                           | 129              | 160              | 171              |         |               |
| Multivariable adjusted <sup>†</sup> | 1                            | 0.83 (0.60–1.16) | 0.89 (0.64–1.22) | 0.99 (0.72–1.38) | .62     |               |
| Boiled method of preparing coffee   |                              |                  |                  |                  |         |               |
| No of cases                         | 9                            | 34               | 41               | 49               |         | .65           |
| Multivariable adjusted <sup>†</sup> | 1                            | 1.45 (0.69–3.04) | 1.28 (0.61–2.66) | 1.36 (0.65–2.84) |         |               |
| <b>Renal cell carcinoma</b>         |                              |                  |                  |                  |         |               |
| All methods of preparing coffee     |                              |                  |                  |                  |         | .66           |
| No of cases                         | 32                           | 72               | 94               | 80               |         |               |
| Multivariable adjusted <sup>†</sup> | 1                            | 0.86 (0.56–1.30) | 0.95 (0.63–1.43) | 0.81 (0.53–1.24) | .46     |               |
| Multivariable adjusted <sup>‡</sup> | 1                            | 0.98 (0.63–1.54) | 1.10 (0.71–1.70) | 0.95 (0.60–1.49) | .84     |               |
| Filtered method of preparing coffee |                              |                  |                  |                  |         |               |
| No of cases                         | 20                           | 57               | 79               | 62               |         |               |
| Multivariable adjusted <sup>†</sup> | 1                            | 0.95 (0.57–1.59) | 1.14 (0.69–1.88) | 0.90 (0.53–1.51) | .97     |               |
| Boiled method of preparing coffee   |                              |                  |                  |                  |         |               |
| No of cases                         | 4                            | 9                | 10               | 13               |         |               |
| Multivariable adjusted <sup>†</sup> | 1                            | 0.90 (0.27–2.95) | 0.76 (0.23–2.49) | 0.93 (0.29–3.03) | .88     |               |

<sup>\*</sup> One 8-oz cup = 237 grams of coffee.

<sup>†</sup> Adjusted for age (continuous), BMI (kg/m<sup>2</sup>, continuous), level of education (high school or less, greater than high school), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (grams/d, continuous), history of diabetes (yes or no), frequency of physical activity in leisure time (<1/wk, 1–2/wk, ≥3/wk), energy (kcal/d, continuous), nutrient density-adjusted fruit consumption (grams/d, continuous), nutrient density-adjusted vegetable consumption (grams/d, continuous).

<sup>‡</sup> Additionally adjusted for coffee preparation method.

lower rates of chronic disease compared to the coffee nondrinkers. Thus, the inverse association with bladder cancer may reflect residual confounding by socioeconomic class or healthy lifestyle. In contrast, ATBC participants were heavy smokers; consequently, a weak inverse association between coffee and bladder cancer may have been masked by residual confounding by smoking. Previously observed adverse associations between coffee drinking and bladder cancer are largely restricted to case-control studies [5], which are more vulnerable to recall and selection bias than cohort studies.

We observed limited evidence for an inverse association between tea drinking and bladder cancer risk. A meta-analysis of eight studies, seven of which were cohort studies, observed a lower risk of bladder cancer among tea drinkers in western countries only [10]. However, another meta-analysis of 25 case-control studies and seven cohort studies found no association for tea drinking overall, or by type (i.e., green or black), with bladder cancer [12]. Similarly, investigators found no association between tea drinking and risk of bladder cancer in a large U.S. cohort study [22].

For RCC, a pooled analysis of 13 prospective studies found suggestive inverse associations for both coffee and tea drinking with RCC [3]. However, a meta-analysis of 16 case-control and 6 cohort studies reported no association between coffee consumption and RCC [24], which is consistent with our findings.

Both coffee and tea contain phenolic compounds with antioxidant potential [11,25] and caffeine, which may alter cell cycle function or induce apoptosis [26]. The inverse, albeit not statistically significant, association between tea and bladder cancer may be due to antioxidants in tea, such as catechins, that are protective against cancer and have been shown to concentrate in the bladder [11]. Catechins have been shown to induce apoptosis, inhibit metastases and angiogenesis, and enhance antioxidant effects [11]. On the other hand, despite detailed adjustment for smoking and other potential confounders, we cannot rule out residual confounding by unknown or poorly measured risk factors such as arsenic in drinking water [13].

Although the data in this study were collected prospectively, mitigating important sources of bias, this study is observational and relied on self-reported consumption; therefore, results should be interpreted with caution. Furthermore, our study assessed diet and lifestyle factors at baseline; thus, we were unable to account for changes in these exposures over the course of follow-up. Coffee and tea consumption were assessed by self-report using an FFQ, which although susceptible to measurement error, has been shown to capture coffee consumption reliably [19,20]. Finally, our study included only male smokers, which is a population at high risk of bladder cancer; however, our results may have limited generalizability. The strengths of this study include the large sample size, the prospective design with extended follow-up and rigorous case ascertainment, the high prevalence of coffee drinking and data on method of coffee preparation, and the collection of detailed data on smoking and other potential confounders.

In summary, we found no association between coffee and tea consumption with RCC. Coffee consumption was also not associated with bladder cancer, although a borderline association between tea drinking and bladder cancer warrants further investigation in diverse populations with higher tea consumption.

## Acknowledgment

The authors express their gratitude to the participants in the ATBC study for their corporation.

This work was supported by the Intramural Research Program of the National Institutes of Health (NIH), United States, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services.

## References

- [1] Sang LX, Chang B, Li XH, Jiang M. Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol* 2013;13:34.

- [2] Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *Int J Cancer* 2012;131:1700–10.
- [3] Lee JE, Hunter DJ, Spiegelman D, Adami HO, Bernstein L, van den Brandt PA, et al. Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies. *Int J Cancer* 2007;121:2246–53.
- [4] Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q. Coffee consumption and bladder cancer: a meta-analysis of observational studies. *Sci Rep* 2015;5:9051.
- [5] Zhou Y, Tian C, Jia C. A dose-response meta-analysis of coffee consumption and bladder cancer. *Prev Med* 2012;55:14–22.
- [6] Lofffield E, Freedman ND, Inoue-Choi M, Graubard BI, Sinha R. A prospective investigation of coffee drinking and bladder cancer incidence in the United States. *Epidemiology* 2017;28:685–93.
- [7] Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. *Eur Urol* 2017;71:96–108.
- [8] Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW, Schilter B. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem Toxicol* 2002;40:1155–63.
- [9] Urgert R, Vanderweg G, Kosmeijerschuil TG, Vandebovenkamp P, Hovenier R, Katan MB. Levels of the cholesterol-elevating diterpenes cafestol and kahweol in various coffee brews. *J Agric Food Chem* 1995;43:2167–72.
- [10] Zhang YF, Xu Q, Lu J, Wang P, Zhang HW, Zhou L, et al. Tea consumption and the incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Eur J Cancer Prev* 2015;24:353–62.
- [11] Conde VR, Alves MG, Oliveira PF, Silva BM. Tea (*Camellia sinensis* (L.)): a putative anticancer agent in bladder carcinoma? *Anticancer Agents Med Chem* 2015;15:26–36.
- [12] Weng H, Zeng XT, Li S, Kwong JS, Liu TZ, Wang XH. Tea consumption and risk of bladder cancer: a dose-response meta-analysis. *Front Physiol* 2016;7:693.
- [13] World Cancer Research Fund/American Institute for Cancer Research. Diet N, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Report 2018. <https://www.wcrf.org/dietandcancer>. [Accessed 17 April 2019].
- [14] Ministry of Foreign Affairs. CBI Trade statistics: coffee. <https://www.cbi.eu/sites/default/files/market.../trade-statistics-coffee-2016.pdf>. [Accessed 7 May 2018].
- [15] The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. The ATBC Cancer Prevention Study Group. *Ann Epidemiol* 1994;4:1–10.
- [16] Kyllonen LE, Teppo L, Lehtonen M. Completeness and accuracy of registration of colorectal cancer in Finland. *Ann Chir Gynaecol* 1987;76:185–90.
- [17] Leinonen MK, Miettinen J, Heikkinen S, Pitkaniemi J, Malila N. Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours. *Eur J Cancer* 2017;77:31–9.
- [18] Korhonen P, Malila N, Pukkala E, Teppo L, Albanes D, Virtamo J. The Finnish Cancer Registry as follow-up source of a large trial cohort—accuracy and delay. *Acta Oncol* 2002;41:381–8.
- [19] Pietinen P, Hartman AM, Haapa E, Rasanen L, Haapakoski J, Palmgren J, et al. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol* 1988;128:655–66.
- [20] Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, et al. The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br J Cancer* 2013;109:1344–51.
- [21] Cumberbatch MG, Cox A, Teare D, Catto JW. Contemporary occupational carcinogen exposure and bladder cancer: a systematic review and meta-analysis. *JAMA Oncol* 2015;1:1282–90.
- [22] Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, et al. Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. *Br J Cancer* 2015;113:809–16.
- [23] Sugiyama K, Sugawara Y, Tomata Y, Nishino Y, Fukao A, Tsuji I. The association between coffee consumption and bladder cancer incidence in a pooled analysis of the Miyagi Cohort Study and Ohsaki Cohort Study. *Eur J Cancer Prev* 2017;26:125–30.
- [24] Wijarnpreecha K, Thongprayoon C, Thamcharoen N, Panjawanatana P, Cheungpasitporn W. Association between coffee consumption and risk of renal cell carcinoma: a meta-analysis. *Intern Med J* 2017;47:1422–32.
- [25] Correa TA, Monteiro MP, Mendes TM, Oliveira DM, Rogero MM, Benites CI, et al. Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant Foods Hum Nutr* 2012;67:277–82.
- [26] Bode AM, Dong Z. The enigmatic effects of caffeine in cell cycle and cancer. *Cancer Lett* 2007;247:26–39.