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A prospective investigation of coffee drinking and bladder cancer incidence in the United States

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Abstract

Background—In 1991, coffee was classified as a Group 2B carcinogen, *possibly carcinogenic to humans*, based on limited epidemiologic evidence of a positive association with bladder cancer. In 2016, the International Agency for Research on Cancer downgraded this classification due to lack of evidence from prospective studies particularly for never smokers.

Methods—Baseline coffee drinking was assessed with a food frequency questionnaire in the NIH-AARP prospective cohort study. Among 469 047 US adults, who were cancer-free at baseline, 6012 bladder cancer cases (5088 men and 924 women) were identified during >6.3 million person years of follow-up. Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), with non-coffee drinkers as the reference group.

Results—Coffee drinking was positively associated with bladder cancer in models adjusted for age and sex (hazard ratio [HR] for 4 cups/day relative to coffee nondrinkers=1.91, 95% CI=1.70–2.14; *P*-trend<0.0001). However, the association was substantially attenuated after adjustment for cigarette smoking and other potential confounders (HR for 4 cups/day relative to coffee nondrinkers=1.18 95% CI=1.05–1.33; *P*-trend=0.0007). Associations were further attenuated after additional adjustment for lifetime smoking patterns among the majority of the cohort with this available data (*P*-trend=0.16). There was no evidence of an association among never smokers (*P*-trend=0.84).

Conclusions—Positive associations between coffee drinking and bladder cancer among ever smokers but not never smokers suggest that residual confounding from imperfect measurement of smoking or unmeasured risk factors may be an explanation for our positive findings.

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Conflicts of interest: None declared

Data availability: An investigator can apply for access to the NIH-AARP Diet & Health Study data using the STaRs system: <https://www.nihaarpstars.com>

The computing code could be obtained from the corresponding author if access to the data was granted.

Keywords

Coffee; urinary bladder neoplasms; bladder cancer

INTRODUCTION

Coffee is one of the most commonly consumed beverages worldwide. It contains over 1000 chemical compounds, many of which, including caffeine, diterpenes, and phenolic acids, are known to be bioactive.¹ Strong inverse associations of coffee drinking with liver cancer² and endometrial cancer^{3, 4} have been consistently observed. However, evidence of an association with other cancers, including breast,⁵ prostate,⁶ and lung⁷ is less consistent. In 1991, the International Agency for Research on Cancer (IARC) Monographs Programme found “*limited evidence* in humans that coffee drinking is carcinogenic in the urinary bladder” and subsequently classified coffee as “*possibly carcinogenic*” to this site (Group 2B; Monographs Volume 51).⁸ According to IARC, *limited evidence* means that confounding, bias, and chance cannot be ruled out as potential explanations for the observed positive association. Subsequent studies have weakened rather than strengthened the evidence for a causal association. In 2016, the IARC Monographs Programme reviewed the accumulated evidence and determined that coffee drinking was “*not classifiable as to its carcinogenicity to humans*” (Group 3; Monographs Volume 116).¹ The 2016 Monograph also highlighted a need for large prospective studies with sufficient case numbers and detailed information on potential confounding factors, such as tobacco smoking, to better understand the association between coffee drinking and bladder cancer, and to help rule out chance, bias, and confounding as possible explanations for previous positive findings.

In the current study, we analyzed data from the NIH-AARP Study, a large prospective cohort study with 469 047 participants and 6012 cases of bladder cancer, nearly eight times as many cases as the combined total of the most recent meta-analysis, which included 753 cases and 236 343 participants.⁹ Our large sample size allowed for stratification by important known risk factors including sex and tobacco smoking. Additionally, more than 15 years of follow-up and detailed information on cigarette smoking use, intensity and time since quitting permitted an assessment of the impact of reverse causality and residual confounding by smoking, respectively.

METHODS

Study population and design

The NIH-AARP Diet and Health Study, which has been described previously,¹⁰ launched in 1995–1996 with the mailing of a self-administered questionnaire to 3.5 million AARP members aged 50 to 71 years who resided in one of six US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) or two US metropolitan areas (Atlanta, Georgia and Detroit, Michigan). The baseline questionnaire queried about demographics, health-related behaviors and dietary intake. The NIH-AARP Diet and Health Study was reviewed and approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Of the 566 398 participants who satisfactorily completed the questionnaire and provided informed consent, we excluded, in order, proxy-responders (n=15 760); those with self-reported cancer (except nonmelanoma skin cancer) prior to baseline (n=49 318); those with self-reported end-stage renal disease prior to baseline (n=997); those with a registry cancer diagnosis prior to baseline (n=2016); those with only a death record for cancer (n=4253); those with missing information on coffee intake (n=2672); those with extremely low or high caloric intake (n=4167), defined as more than two interquartile ranges above the sex-specific 75th percentile or below the 25th percentile of intake; those who died or were diagnosed with bladder cancer on or before the date their questionnaire was received (n=32); and those with missing information on cigarette smoking (n=18 136). The resulting analytic cohort consisted of 279 290 men and 189 757 women (N=469 047).

Cohort Follow-up

Follow-up time accumulated from the date the baseline questionnaire was returned (beginning October 25, 1995) until the date of first urinary system cancer, the date of death, the date the participant moved out of the catchment area, or the end of study follow-up (December 31, 2011), whichever came first. Vital status was ascertained by linkage to the Social Security Administration Death Master File and response to mailings. Participant addresses were updated annually in response to change of address requests and by matching cohort participants to the US Post Office National Change of Address database.

Case ascertainment

We identified incident bladder cancer cases by probabilistic linkage of the NIH-AARP Diet and Health Study cohort to cancer registries of the eight baseline states and three additional states (Arizona, Texas, and Nevada) to which participants were most likely to move during follow-up. A validation study of the eight baseline cancer registries estimated that this approach ascertained about 90% of all cancer cases.¹¹ Bladder cancer cases were defined according to the *International Classification of Diseases for Oncology (ICD-O, 3rd edition)*¹² by anatomic site C67.0–C67.9 and transitional cell (urothelial) morphology (ICD codes 8120, 8122, 8123, or 8130).

Exposure assessment

The self-administered baseline questionnaire included a 124-item food frequency questionnaire (FFQ) that queried about usual coffee intake in the previous 12 months using ten predefined frequency categories, ranging from none to 6 cups/day. Of those who reported drinking coffee, 96% (n=452 386) provided information on whether they drank caffeinated or decaffeinated coffee more than half the time. We used responses to these two FFQ items to categorize coffee drinkers into pre-specified categories ranging from none to 4 cups/day for total coffee and for either caffeinated or decaffeinated coffee more than half the time. For participants with missing information on coffee type, we created a missing category.

The baseline questionnaire also provided information on potential confounding factors. Smoking history was defined as never (<100 cigarettes during lifetime), former, or current smoker. Current and former smokers further reported smoking intensity using six categories

of cigarettes/day (1–10, 11–20, 21–30, 31–40, 41–60, and ≥61), and former smokers additionally reported time since quitting using four categories (quit <1 year ago, quit 1–4 years ago, quit 5–9 years ago, and quit ≥10 years ago). We defined former smokers as those who had quit ≥1 year prior to baseline. Prior methodological studies have shown that the assessment of tobacco smoking via questionnaire is reproducible and valid.^{13, 14} A separate question assessed regular (≥1 year) use of pipes or cigars. Average daily alcohol intake over the last 12 months was calculated from drinks of alcohol from beer, wine, and liquor. Nutrient and food group intakes were estimated using FFQ responses in conjunction with a nutrient and food group database developed using national dietary intake data from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intake by Individuals¹⁵. Physical activity over the last 12 months was defined as frequency of activity lasting ≥20 minutes that caused increases in breathing or heart rate or sweating. Body mass index (BMI) was calculated from self-reported height and weight at baseline.

Statistical methods

We tabulated demographic and lifestyle factors, potentially associated with bladder cancer, by coffee intake separately among men and women because sex is an important risk factor for bladder cancer. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for categories of coffee intake and bladder cancer using non-drinkers of coffee as the referent group. We conducted tests for linear trend across categories of coffee intake by assigning participants the midpoint of their coffee intake category and entering this single variable into a separate model. Participants in the ≥4 cups/day category were assigned a value of 5 cups/day. The risk estimate for the continuous value (1 cup/day increase) was based on the original 10-category variable; each category was assigned its midpoint value, and participants in the highest category of intake (i.e., ≥6 cups/day) were assigned a value of 6 cups/day. In our primary analysis, we compared overall models, adjusted for age and sex, and sex-stratified models adjusted for age with those additionally adjusted for tobacco smoking and other potential confounding factors. Only age and cigarette smoking altered risk estimates by more than 5%. For the less than 5% of the cohort that was missing data for a particular covariate, an indicator variable for missing was included in the models. To test for sex-heterogeneity and smoking-heterogeneity in the association between coffee intake and bladder cancer risk, we compared multivariable models with and without the cross-product terms for either sex or each-level of smoking (never, current, or former) and coffee intake (continuous) using the likelihood ratio test. Person-time was used as the underlying time metric; results calculated with age as the underlying time metric were similar. Consistent with the assumption of proportional hazards, inclusion of the time dependent interaction did not improve the model fit (P -value for interaction=0.98). We used SAS software, version 9.3 (SAS Institute, Cary, NC) to conduct our analyses.

To explore the impact of cigarette smoking on risk estimates, we stratified by detailed smoking categories, including categories of smoking dose among current smokers, and categories of smoking dose and time since quitting among former smokers. Next, we further explored the impact of residual confounding by cigarette smoking in a subset of participants ($n=250\ 716$) who provided information on cigarette smoking use and intensity over the

lifetime in the 2004–2005 follow-up questionnaire. We compared the HRs from the multivariable-adjusted baseline model to those additionally adjusted for cigarette smoking status and, if applicable, the number of cigarettes per day, on average, during the following age-periods: <15, 15 to 19, 20 to 24, 25 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 60 and 70 years old.

In additional secondary analyses, we estimated the HRs for those who predominantly drank caffeinated-coffee or decaffeinated coffee. Caffeinated and decaffeinated coffee variables as well as an indicator variable for missing caffeine-type were included in a single model, and non-drinkers of either type of coffee served as the reference group. Lastly, we explored the potential for reverse causation by evaluating associations of coffee drinking with bladder cancer cases that occurred less than 5 years, 5 to less than 10 years, or 10 or more years after baseline.

RESULTS

During more than 6.3 million person years of follow-up, 6012 incident cases of bladder cancer (5088 men and 924 women) were identified. The median age at baseline was 62.7 years and 62.3 years for men and women, respectively. Median follow-up time was 15.5 years. The cohort was predominantly non-Hispanic White (92%) and was well educated (67% of men and 55% of women had at least some college education). A majority of men (70%) and women (54%) had a history of smoking cigarettes; however, most, 57% of men and 38% of women, were former smokers. Coffee intake was positively correlated with smoking intensity among current smokers (Spearman correlation coefficient=0.18, $P<0.0001$). Approximately 91% of men and 88% of women reported drinking coffee and 60% of men and 52% of women reported drinking at least 2 cups/day. At baseline, individuals who reported higher coffee intakes were more likely to be men than women, non-Hispanic White than other races, and ever than never smokers (Table 1); each of which is a known risk factor for bladder cancer.

First, we tested the hypothesis that higher coffee intake is associated with increased risk of bladder cancer (Table 2). Overall, higher coffee intake was associated with greater risk of bladder cancer in age- and sex-adjusted models; the HR for the highest category of coffee intake (≥4 cups/day) relative to who did not drink coffee was 1.91 (95% CI=1.70, 2.14; P -trend<0.0001). Following adjustment for smoking, a positive, albeit attenuated, association remained between coffee intake and bladder cancer (HR for ≥4 cups/day=1.21, 95% CI=1.07, 1.36; P -trend=0.0001). In sex-stratified analyses, adjustment for smoking similarly attenuated the positive association for ≥4 cups/day from a relative risk of 2.04 (95% CI=1.79–2.32) to 1.29 (95% CI=1.13–1.47) among men and from a relative risk of 1.57 (95% CI=1.22–2.02) to 0.98 (95% CI=0.76–1.27) among women. Despite the observed differences in risk estimates for men and women, we did not find evidence of effect modification by sex (P for sex heterogeneity=0.92). Further adjustment for other potential confounders did not meaningfully alter risk estimates (Table 2).

In analyses stratified by tobacco smoking status (Table 3), we found evidence that risk estimates varied by smoking status (P for smoking heterogeneity=0.03). We observed

evidence of positive associations among both lower intensity (i.e., ≤ 20 cigarettes/day) current smokers (P -trend=0.01) and higher intensity (i.e., >20 cigarettes/day) current smokers (P -trend=0.02), but we found no evidence of an association between coffee drinking and bladder cancer risk among never smokers (HR for ≤ 4 cups/day =0.87, 95% CI=0.65–1.17; P -trend=0.84). No clear pattern was observed among former smokers, although most risk estimates were moderately above one. Additionally, the exclusion of participants who ever reported regularly smoking pipes or cigars, did not meaningfully alter risk estimates (eTable 1). Next, we evaluated the association of coffee drinking and bladder cancer in the majority of participants with additional information on lifetime cigarette use. In Table 4, we show that adjustment for both baseline tobacco smoking variables (i.e., cigarette smoking status, intensity, time since quitting among former smokers, and cigar/pipe smoking status) and cigarette smoking use and intensity in each age group, including younger ages, further attenuated positive risk estimates. In the final multivariable-adjusted model the relative risk for ≤ 4 cups/day was 1.09 (95% CI=0.93–1.29; P -trend=0.16).

Associations were similar for both caffeinated and decaffeinated coffee and were also considerably attenuated after adjustment for tobacco smoking (eTable 2). Nevertheless, a positive association between the highest level of coffee intake (≥ 4 cups/day), either caffeinated or decaffeinated, and bladder cancer risk (HR=1.20, 95% CI=1.06–1.35 and HR=1.18, 95% CI=1.00–1.38, respectively) persisted. Finally, our examination of risk estimates over follow-up time suggested slightly stronger associations for cases that were diagnosed within 5 years of baseline, although we found no evidence of a violation of the proportional hazard assumption (P for interaction=0.98; eTable 3) indicating that risk estimates did not vary meaningfully by follow-up time.

DISCUSSION

This prospective analysis included, to our knowledge, the largest number of bladder cancer cases to date and examined the association of coffee drinking and bladder cancer risk stratified by cigarette smoking, an important risk factor for bladder cancer.¹⁶ Overall, we observed a modest increased risk of bladder cancer among coffee drinkers as compared with those who did not drink coffee. However, this positive association was restricted to ever smokers, particularly current smokers, and we observed no evidence of an association among never smokers. Previous prospective cohort studies, conducted in the United States, Europe, and Asia, with smoking-adjusted analyses have provided little evidence for a positive, independent, dose-response relationship between coffee drinking and risk of bladder cancer,^{17–24} and two studies observed inverse associations among adults in Japan²⁵ and women in the Netherlands.²⁶ Nevertheless, positive associations in case-control studies,²⁷ which are difficult to interpret due to potential recall and selection bias, as well as suggestive, but imprecise positive trends in some cohort studies^{20, 22, 24, 26} have sustained speculation that coffee drinking causes bladder cancer. Importantly, the few cohort studies that have conducted sensitivity analyses among never smokers have had very limited case numbers in this subgroup, and risk estimates have been imprecise and inconsistent.^{20, 25, 26}

Smoking is a strong risk factor for bladder cancer in both men and women in the NIH-AARP cohort with a relative risk estimate of 2.22 (95% CI=2.03–2.44) and 4.06 (95%

CI=3.66–4.50) for former and current smokers as compared with never smokers, respectively.¹⁶ In the NIH-AARP cohort and in the overall US population²⁸ smoking is positively correlated with coffee drinking. One possible explanation is that the cytochrome P450 1A2 (CYP1A2) metabolic pathway is upregulated by both caffeine and compounds in tobacco smoke, including nicotine and polycyclic aromatic hydrocarbons^{29–31} such that the effect of caffeine is potentially weaker among heavier smokers leading them to drink more coffee than nonsmokers.

Because of this strong positive correlation between coffee drinking and tobacco smoking, associations between coffee drinking and bladder cancer are potentially confounded by smoking even if it is adjusted for in multivariable models. It is, therefore, important to evaluate whether the modest association we observed for coffee drinking and bladder cancer may be due to residual confounding by smoking. Thus, we investigated potential residual confounding using a multifaceted approach.³² First, we found that age- and sex-adjusted relative risks were substantially attenuated following detailed adjustment for baseline tobacco smoking. Our adjustment for smoking was probably imperfect owing to misclassification, which occurs because true tobacco smoke exposure is not accurately captured via self-report for reasons including but not limited to poor recall, differences in smoking practices (e.g., depth of inhalation or number of inhalations), changes during follow-up, or differences in second-hand smoke exposure. To quantify the impact of residual confounding resulting from confounder misclassification, we applied a method developed by Savitz and Barón.³³ Assuming a true (i.e. the completely adjusted) relative risk of 1.00, we estimated that 69% of confounding was removed by adjustment for baseline tobacco smoking in our study. We treated the age- and sex-adjusted HR for a 1 cup/day increase in coffee intake (HR=1.13) as the crude risk estimate and the HR with additional adjustment for smoking (HR=1.04) as the partially adjusted risk estimate in our percent adjustment calculation ($[(1.13 - 1.04)/(1.13 - 1.00) \times 100] = 69\%$). A relatively small degree of tobacco smoking misclassification, (i.e., approximately 91% sensitivity and 91% specificity), would result in the modest associations of coffee drinking with bladder cancer risk that we observed in NIH-AARP cohort.³³ Strengthening our hypothesis for residual confounding, associations for coffee drinking and bladder cancer were larger in men than in women, and men were nearly twice as likely as women to be ever smokers. Moreover, among ever smokers, men were more than twice as likely as women to have smoked >40 cigarettes/day. Second, in smoking-stratified analyses, we showed that risk estimates for never smokers were close to or even below one, and that risk estimates for former smokers were weaker than those for current smokers, which is consistent with residual confounding by smoking. Finally, we found that additional adjustment for smoking history, among a subgroup of participants with detailed information on lifetime cigarette smoking use and intensity, resulted in further attenuation of risk estimates.

Limitations of this study include its observational design, the use of self-reported data on coffee intake, which is prone to measurement error potentially attenuating risk estimates, and a lack of data on some suspected bladder cancer risk factors. More specifically, the observed positive associations could reflect confounding by factors that were not measured in our cohort including aspects of smoking, like depth of inhalation and secondhand smoke exposure, or occupations in which workers were exposed to bladder cancer carcinogens such

as aromatic amines (e.g. rubber workers and painters) or polycyclic aromatic hydrocarbons (e.g. metal, machine and automobile workers).³⁴ In fact, the relative prevalence of an unmeasured confounder would only have to be slightly higher among coffee drinkers than coffee nondrinkers to explain the observed association.^{35, 36} Other possible explanations include chance or a real positive association.

In conclusion, our study, with more than 6000 cases, is the largest prospective study of coffee and bladder cancer to date, and we observed little evidence for a strong association. We found a modest positive association between coffee drinking and bladder cancer; however, adjustment for cigarette smoking substantially attenuated risk estimates, and there was no evidence of an association among never smokers suggesting that residual confounding from imperfect measurement of smoking may explain our positive findings. Future pooled or meta-analyses should further explore the association of coffee drinking with bladder cancer among never smokers and confounding by occupational exposures, particularly among men. Coffee is widely consumed throughout the world; thus, it is vital that assessments of its carcinogenicity in humans are based on well-conducted, prospective cohort studies with sufficient case numbers and adequate control for important confounding factors like tobacco smoking.¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline characteristics of the NIH-AARP Diet and Health Study by sex and coffee intake ($N = 469\ 047$)

Characteristic	Coffee intake (cups/day)									
	Men (n= 279 290)					Women (n= 189 757)				
	None	1	2 to 3	4	Overall	None	1	2 to 3	4	Overall
No. subjects (%)	25 093	86 442	118 143	49 612	279 290	23 080	68 267	74 128	24 282	189 757
No. bladder cancers (%)	286 (1.1)	1390 (1.6)	2319 (2.0)	1093 (2.2)	5088 (1.8)	97 (0.4)	266 (0.4)	401 (0.5)	160 (0.7)	924 (0.5)
Age (years), mean (SD)	61.4 (5.5)	62.6 (5.3)	62.3 (5.3)	61.2 (5.4)	62.1 (5.4)	61.1 (5.6)	62.1 (5.4)	62.0 (5.3)	61.4 (5.4)	61.8 (5.4)
Caffeinated coffee, % ^a	0	52.0	69.5	76.3	59.1	0.0	47.3	67.7	74.6	53.0
Decaffeinated coffee, (%) ^a	0	42.3	27.6	20.8	28.5	0.0	47.2	29.1	21.9	31.2
Cigarette smoking status, % ^b										
Never ^c	50.7	31.7	20.1	12.1	25.0	62.3	52.3	40.5	26.9	45.6
Former	39.4	55.7	61.8	57.2	57.1	28.5	37.6	41.5	35.4	37.8
Current	5.3	7.1	12.4	25.8	12.5	9.2	10.0	18.0	37.7	16.6
Cigarettes smoked per day, % (n= 194 367) ^d										
10	25.5	26.0	19.0	12.7	20.0	37.8	42.5	35.6	23.8	35.9
11 to 20	30.3	32.9	32.8	29.1	31.9	31.0	31.2	35.0	37.9	34.0
21 to 40	32.5	31.0	36.9	42.5	36.2	25.3	21.6	24.8	32.2	25.1
>40	11.7	10.2	11.3	15.8	12.0	6.0	4.6	4.6	6.1	5.0
Years since quitting smoking, % (n= 159 437) ^e										
10	84.9	82.8	79.6	73.3	79.8	75.1	73.2	68.9	62.4	70.2
5 to 9	9.8	11.4	13.4	16.1	13.1	15.4	17.4	19.0	20.8	18.3
1 to 4	5.4	5.8	7.0	10.6	7.2	9.6	9.5	12.0	16.9	11.5
Ever smokers of pipes or cigars, %	17.9	25.3	30.3	34.3	28.4	0.3	0.4	0.4	0.6	0.4
Non-Hispanic White, %	90.4	89.3	94.6	96.2	92.8	88.4	85.0	92.8	95.5	89.8
Family history of cancer, %	46.1	46.3	47.8	48.7	47.3	51.2	50.6	52.1	52.9	51.6
College graduate, %	50.9	46.2	44.2	41.1	44.9	32.2	31.2	29.3	26.4	30.0
Self-reported diabetes, %	10.0	10.8	9.8	9.6	10.1	9.0	8.6	6.2	5.3	7.3
Alcohol, 3 drinks/day, %	6.1	9.2	12.3	12.5	10.8	1.8	2.3	3.1	3.2	2.7
Vigorous physical activity 5 times/week	25.0	21.6	20.8	20.0	21.3	17.7	16.2	15.8	15.6	16.2

Characteristic	Coffee intake (cups/day)									
	Men (n= 279 290)					Women (n= 189 757)				
	None	1	2 to 3	4	Overall	None	1	2 to 3	4	Overall
Fair or poor self-reported general health, %	11.5	13.1	10.7	11.1	11.6	15.3	14.2	10.5	10.8	12.4
Body mass index (kg/m ²), mean (SD)	27.1 (4.7)	27.1 (4.4)	27.3 (4.2)	27.4 (4.3)	27.3 (4.3)	27.5 (6.7)	27.2 (6.3)	26.6 (5.6)	26.2 (5.9)	26.8 (6.0)
Energy (kcal/day), mean (SD)	1994 (853)	1929 (822)	2006 (818)	2198 (906)	2015 (844)	1565 (685)	1536 (655)	1570 (632)	1681 (695)	1572 (656)
Vegetable intake (servings/day), mean (SD)	2.1 (1.2)	2.1 (1.1)	2.0 (1.0)	1.9 (1.0)	2.0 (1.0)	2.5 (1.5)	2.5 (1.4)	2.5 (1.2)	2.4 (1.3)	2.5 (1.3)
Fruit intake (servings/day), mean (SD)	1.8 (1.3)	1.8 (1.2)	1.5 (1.0)	1.3 (1.0)	1.6 (1.1)	2.1 (1.4)	2.1 (1.3)	1.8 (1.2)	1.6 (1.1)	1.9 (1.3)

NIH-AARP, National Institutes of Health-AARP; SD, standard deviation

^aType of coffee consumed (caffeinated or decaffeinated) among coffee drinkers was based on the type of coffee the participant reported drinking more than half the time. Due to missing data on caffeine type, coffee consumption does not sum to 100% for coffee intake categories

^bIndividuals who smoked pipes or cigars but not cigarettes contribute to the denominator but not the numerator

^cNever smokers of any tobacco products (cigarettes, pipes, cigars)

^dCurrent and former smokers

^eFormer smokers

Table 2

Hazard ratios (95% confidence intervals) for bladder cancer according to coffee intake in the NIH-AARP Diet and Health Study by sex

Model adjustments	Coffee Intake (cups/day)					P-trend	P sex-heterogeneity ^d
	1 cup/day increase	None (ref.) ^a	1	2 to 3	4		
Overall (N= 469 047)							0.92
No. cases	6012	383	1656	2720	1253		
Age, sex	1.13 (1.11–1.15)	1.00	1.20 (1.08–1.35)	1.53 (1.38–1.70)	1.91 (1.70–2.14)	<0.0001	
Age, sex, smoking ^b	1.04 (1.02–1.05)	1.00	1.07 (0.96–1.20)	1.17 (1.05–1.31)	1.21 (1.07–1.36)	0.0001	
Multivariable-adjusted ^c	1.03 (1.01–1.05)	1.00	1.05 (0.94–1.18)	1.13 (1.02–1.27)	1.18 (1.05–1.33)	0.0007	
Men (n= 279 290)							
No. cases	5088	286	1390	2319	1093		
Age	1.13 (1.11–1.15)	1.00	1.31 (1.16–1.49)	1.64 (1.45–1.85)	2.04 (1.79–2.32)	<0.0001	
Age, smoking ^b	1.04 (1.02–1.06)	1.00	1.16 (1.02–1.31)	1.25 (1.10–1.41)	1.29 (1.13–1.47)	0.0004	
Multivariable-adjusted ^c	1.03 (1.01–1.05)	1.00	1.14 (1.00–1.29)	1.20 (1.06–1.36)	1.25 (1.09–1.43)	0.002	
Women (n= 189 757)							
No. cases	924	97	266	401	160		
Age	1.13 (1.08–1.17)	1.00	0.87 (0.69–1.10)	1.21 (0.97–1.51)	1.57 (1.22–2.02)	<0.0001	
Age, smoking ^b	1.03 (0.98–1.07)	1.00	0.81 (0.64–1.02)	0.96 (0.77–1.20)	0.98 (0.76–1.27)	0.13	
Multivariable-adjusted ^c	1.03 (0.98–1.07)	1.00	0.79 (0.62–1.00)	0.93 (0.74–1.17)	0.97 (0.74–1.26)	0.13	

^aReferent group was non-drinkers of coffee

^bSmoking adjustment included baseline cigarette smoking status (current, former, or never), number of cigarettes smoked per day (1–10, 11–20, 21–30, 31–40, 41–60, or ≥60), time since quitting among former smokers (1 to 4, 5 to 9, or ≥10 years before baseline), and having ever smoked pipes or cigars (yes or no)

^cMultivariable models adjusted for age at study baseline (continuous), sex, smoking^b, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or Asian/Pacific Islander/American Indian/Alaskan Native), body mass index (<18.5, 18.5 to <25, 25 to <30, or ≥30 kg/m²), level of education (high school graduate, some college, or college graduate), alcohol consumption (0, <1, 1–2, or ≥3 drinks/day), self-reported general health status (excellent/very good, good, or fair/poor), total energy intake (kcal/day, continuous), nutrient density-adjusted fruit intake (servings/day, continuous), nutrient-density-adjusted vegetable intake (servings/day, continuous), supplement use (yes or no), physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week), history of diabetes (yes or no), and family history of cancer (yes or no)

^dP-value for likelihood ratio test comparing models with and without cross-product term for sex and continuous coffee drinking variable

Hazard ratios (95% confidence intervals) for bladder cancer according to coffee intake in the NIH-AARP Diet and Health Study by smoking ($N = 453$ 935)^a

Smoking subgroup (<i>n</i>)	Cigarettes/day (<i>n</i>)	1 cup/day increase	None (ref.) ^b	Coffee Intake (cups/day)			<i>P</i> -trend	<i>P</i> smoking-heterogeneity ^f
				1	2 to 3	4		
Never smoker (<i>n</i>=156 448)^a	No. cases	890	151	336	337	66		0.03
	HR (95% CI) ^c	1.01 (0.96–1.06)	1.00	0.91 (0.75–1.11)	1.03 (0.85–1.26)	0.87 (0.65–1.17)	0.84	
	No. cases	3676	184	1095	1709	688		
	HR (95% CI) ^{c,d,e}	1.02 (1.00–1.05)	1.00	1.15 (0.98–1.34)	1.14 (0.98–1.33)	1.23 (1.04–1.33)	0.07	
Former smoker (<i>n</i>=231 084)	No. cases	1256	73	457	565	161		
	HR (95% CI) ^{c,d}	1.02 (0.98–1.06)	1.00	1.20 (0.93–1.53)	1.14 (0.89–1.46)	1.20 (0.91–1.58)	0.83	
	No. cases	1431	74	402	660	295		
	HR (95% CI) ^{c,d}	1.02 (0.99–1.06)	1.00	1.12 (0.88–1.44)	1.08 (0.85–1.38)	1.23 (0.95–1.59)	0.18	
Quit 5 to 9 years ago	No. cases	210	10	54	110	36		
	HR (95% CI) ^{c,d}	1.06 (0.97–1.17)	1.00	0.90 (0.46–1.77)	1.18 (0.61–2.27)	1.17 (0.58–2.39)	0.18	
	No. cases	406	14	91	203	98		
	HR (95% CI) ^{c,d}	1.02 (0.96–1.09)	1.00	1.04 (0.59–1.83)	1.17 (0.68–2.03)	1.13 (0.64–1.99)	0.53	
Quit 1 to 4 years ago	No. cases	148	3	42	72	31		
	HR (95% CI) ^{c,d}	1.07 (0.96–1.18)	1.00	2.67 (0.82–8.65)	2.83 (0.89–9.05)	2.97 (0.90–9.77)	0.31	
	No. cases	225	10	49	99	67		
	HR (95% CI) ^{c,d}	1.01 (0.93–1.10)	1.00	1.02 (0.51–2.02)	0.96 (0.50–1.85)	1.06 (0.54–2.09)	0.76	
Current smoker (<i>n</i>=66 403)	No. cases	1262	41	166	588	467		
	HR (95% CI) ^{c,d}	1.05 (1.02–1.09)	1.00	0.91 (0.64–1.28)	1.33 (0.97–1.83)	1.32 (0.95–1.81)	0.001	
	No. cases	731	25	120	361	225		
	HR (95% CI) ^{c,d}	1.05 (1.00–1.10)	1.00	0.95 (0.62–1.46)	1.32 (0.88–1.99)	1.31 (0.86–1.98)	0.01	
>20 (23 423)	No. cases	531	16	46	227	242		
	HR (95% CI) ^{c,d}	1.05 (1.00–1.11)	1.00	0.83 (0.47–1.47)	1.34 (0.80–2.23)	1.32 (0.80–2.20)	0.02	

^aParticipants who reported never smoking cigarettes but who reported smoking pipes/cigars ($n = 15$ 112) were excluded from this analysis

^bReferent group was non-drinkers of coffee

^c Adjusted for age at study baseline (continuous), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or Asian/Pacific Islander/American Indian/Alaskan Native), body mass index (<18.5, 18.5 to <25, 25 to <30, or ≥30 kg/m²), level of education (high school graduate, some college, or college graduate), alcohol consumption (0, <1, 1–2, or ≥3 drinks/day), self-reported general health status (excellent/very good, good, or fair/poor), total energy intake (kcal/day, continuous), nutrient density-adjusted fruit intake (servings/day, continuous), nutrient density-adjusted vegetable intake (servings/day, continuous), supplement use (yes or no), physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5 times/week), history of diabetes (yes or no), and family history of cancer (yes or no)

^d Additionally adjusted for having ever smoked pipes or cigars (yes or no), number of cigarettes smoked per day (1–10, 11–20, 21–30, 31–40, 41–60, or ≥60)

^e Additionally adjusted for time since quitting (1 to 4, 5 to 9, or ≥10 years before baseline)

^f P-value for likelihood ratio test comparing models with and without cross-product terms for 3-level smoking variable (never, former, or current) and continuous coffee drinking variable

Table 4

Hazard ratios (95% confidence intervals) for bladder cancer according to coffee intake in the NIH-AARP Diet and Health Study among those with information on lifetime cigarette smoking intensity ($N = 250\ 716$)

Model adjustments	1 cup/day increase	Coffee Intake (cups/day)			P-trend
		None (ref.) ^a	1	2 to 3	4
No. cases	3263	210	889	1528	636
Age and sex ^b	1.12 (1.10–1.15)	1.00	1.22 (1.05–1.42)	1.60 (1.39–1.85)	1.84 (1.57–2.15)
Baseline tobacco smoking ^{b,c}	1.03 (1.01–1.05)	1.00	1.07 (0.92–1.25)	1.22 (1.06–1.42)	1.17 (0.99–1.37)
Cigarette smoking use and intensity in each age group ^{b,d}	1.04 (1.01–1.06)	1.00	1.06 (0.91–1.23)	1.21 (1.04–1.40)	1.18 (1.01–1.39)
Baseline tobacco smoking and cigarette smoking use and intensity in each age group ^{b,c,d}	1.02 (1.00–1.05)	1.00	1.06 (0.91–1.23)	1.19 (1.03–1.38)	1.13 (0.96–1.32)
Final multivariable-adjusted ^{b,c,d,e}	1.02 (1.00–1.04)	1.00	1.05 (0.90–1.22)	1.15 (0.99–1.34)	1.09 (0.93–1.29)

^aReferent group was non-drinkers of coffee

^bAdjusted for age at study baseline (continuous) and sex

^cAdditionally adjusted for baseline cigarette smoking, which was defined as number of cigarettes smoked per day (1–10, 11–20, 21–30, 31–40, 41–60, or 60) among current and former smokers, and time since quitting among former smokers (1 to 4, 5 to 9, or 10 years before baseline), and having ever smoked pipes or cigars (yes or no)

^dAdditionally adjusted for cigarettes smoked per day (none, less than 1, 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or 60) by age group (less than 15 years old, 15 to 19 years old, 20 to 24 years old, 25 to 29 years old, 30 to 39 years old, 40 to 49 years old, 50 to 59 years old, 60 to 69 years old, and 70 years and older)

^eAdditionally adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or Asian/Pacific Islander/American Indian/Alaskan Native), body mass index (<18.5, 18.5 to <25, 25 to <30, or 30 kg/m²), level of education (high school graduate, some college, or college graduate), alcohol consumption (0, <1, 1–2, or 3 drinks/day), self-reported general health status (excellent/very good, good, or fair/poor), total energy intake (kcal/day, continuous), nutrient density-adjusted fruit intake (servings/day, continuous), nutrient density-adjusted vegetable intake (servings/day, continuous), supplement use (yes or no), physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5 times/week), history of diabetes (yes or no), and family history of cancer (yes or no)