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Coffee consumption and the risk of overall and fatal prostate cancer in the NIH-AARP Diet and Health study

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Abstract

Purpose—Evidence on the association between coffee consumption and prostate cancer risk is inconsistent; furthermore, few studies have examined the relationship between coffee consumption and fatal prostate cancer. The aim of this study was to investigate whether coffee intake is associated with the risk of overall and fatal prostate cancer.

Methods—We conducted a prospective analysis among 288,391 men in the National Institutes of Health (NIH)-AARP Diet and Health Study who were between 50–71 years old at baseline in 1995–96. Coffee consumption was assessed at baseline. Cox proportional hazards models were used to calculate the age- and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI).

Results—Over 11 years of follow-up, 23,335 cases of prostate cancer were ascertained, including 2,927 advanced and 917 fatal cases. Coffee consumption was not significantly

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associated with prostate cancer risk. The multivariable-adjusted HRs (95% CI), comparing those who drank six or more cups per day to non-drinker were; 0.94 (0.86–1.02), p-trend=0.08 for overall prostate cancer, 1.13 (0.91–1.40), p-trend=0.62 for advanced prostate cancer and 0.79 (0.53–1.17), p-trend=0.20 for fatal prostate cancer. The findings remained nonsignificant when we stratified by prostate specific antigen (PSA) testing history or restricted to non-smokers.

Conclusions—We found no statistically significant association between coffee consumption and the risk of overall, advanced or fatal prostate cancer in this cohort, though a modest reduction in risk could not be excluded.

Keywords

Coffee; caffeine; prostatic neoplasms; prospective studies

Introduction

Coffee contains multiple chemical compounds that are known to have biological activity and some of these compounds may have potentially beneficial effects (1). Long-term coffee intake has been consistently associated with lower risk of type 2 diabetes, better glucose metabolism and lower insulin levels (2, 3). Coffee could affect the risk of prostate cancer through the antioxidant and anti-inflammatory effects of its beneficial components including lignans, phytoestrogens and chlorogenic acids (4–6). Coffee has also been associated with lower levels of IGF-1 and circulating sex hormones which are associated with prostate cancer progression (7, 8).

Epidemiological evidence of the relationship between coffee consumption and prostate cancer is inconsistent. Several prospective studies found no significant association between coffee intake and risk of prostate cancer (9–12). However, many of these adjusted for only a few confounding factors and lacked information on disease stage and grade. Adjustment for smoking is particularly important since smoking is linked with increased coffee intake in many populations, and is independently associated with higher risk of prostate cancer mortality (13, 14). A meta-analysis of five cohort studies reported an inverse association between coffee consumption and overall prostate cancer risk, with a summary estimate of 0.76 (95% confidence interval (CI) 0.61, 0.98) for highest drinkers vs. non/low drinkers (15). A recent study reported a marked decrease in risk of lethal (but not overall) prostate cancer (8).

The aim of our analysis was to examine the association between coffee consumption and risk of fatal, advanced and overall prostate cancer in a large cohort with long follow up and information on multiple potential confounders.

Methods

Study population

The NIH-AARP Diet and Health Study was initiated in 1995–1996, when AARP members aged 50 to 71 years old residing in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta and Detroit) responded to a questionnaire eliciting information on dietary behaviors, demographic characteristics and other health-related information (n=566,398) (16). Completion of the self-administered questionnaire was considered to imply informed consent to participate in the study. In a subsequent mailed questionnaire (1996–1997, 69% response rate) participants reported their history of prostate specific antigen (PSA) testing and digital rectal examinations during the previous three years. For our analyses, we excluded 14,495 men whose questionnaires were completed by others, as well as 27,270 with cancer other than

nonmelanoma skin cancer at baseline, 626 with self-reported kidney failure, 2,575 who reported extreme intake of total energy (exceeding twice the interquartile ranges of log-transformed intake), 1,273 with missing coffee intake information, and 5,036 who died in the first 2 years of follow-up, leaving an analysis dataset of 288,391 men. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Assessment of exposure

At baseline, participants completed a 124-item food frequency questionnaire that assessed dietary intake over the previous 12 months, including caffeine containing drinks such as coffee, tea and soft drinks (17). Consumption was assessed in frequency categories ranging from 0 to 6 or more cups per day and almost 90% of coffee drinkers provided information on whether they drank caffeinated or decaffeinated coffee more than half the time. The questionnaire also included foods that contain small amounts of caffeine. Total daily caffeine intake was calculated based on the food items, portion sizes and nutrient database constructed using the US Department of Agriculture's 1994–1996 Continuous Survey of Food Intake by Individuals (18). The FFQ was validated in a subset of the study population using two non-consecutive 24-hour recalls (19), the correlation coefficient for coffee consumption between the two assessment methods was 0.8 (20).

Ascertainment and classification of prostate cancer

Study participants were followed by means of linkage to the National Change of Address database maintained by the US Postal Service, specific change-of-address requests from participants, and updated addresses returned during other mailings. Incident prostate cancer cases were identified through linkage with eleven state cancer registry databases (eight original and three additional states – Arizona, Nevada and Texas). Vital status was assessed by periodic linkage to the Social Security Administration Death Master File on deaths in the US, follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings. Details on the cohort design and maintenance have been described previously (16).

Information on prostate cancer stage was obtained from the registries. We defined advanced cases as those whose cancer had spread beyond the prostate, with a clinical classification of T3-T4, N1 or M1 according the Tumor-Node-Metastasis classification system or those that subsequently died of prostate cancer during follow up. Fatal cases, a subset of advanced cases, were those who died of prostate cancer during follow-up. Nonadvanced cases were those involving the prostate gland only (classification of T1a - T2b, N0, and M0)

Statistical analysis

Person-years of follow-up were calculated from return of baseline questionnaire to diagnosis of any cancer, move out of the cancer registry area, death, or the end of follow-up, whichever came first. Participants were followed for incidence until December 31, 2006 and for death until December 31, 2008. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for coffee intake categories (none, < 1, 1, 2–3, 4–5, and ≥ 6 cups/day). The proportional hazards assumption was tested and confirmed by modeling an interaction of follow-up time with coffee consumption. Tests of linear trend across categories of coffee consumption were performed by modeling the categories as continuous variables using the median intake for each category.

The multivariate models were adjusted for potential confounding by prostate cancer risk factors previously identified in this cohort and in other studies including race (white, black,

other), age (continuous), height (quartiles), body mass index (BMI) (<18.5, 18.5 to 25, >25–30, >30 – 35, >35 kg/m^2), physical activity (never or rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, or 5+ times per week), smoking status (never, past quit >10 years, past quit <10 years ≤ 20 cigarettes/day, past quit <10 years >20 cigarettes/day, current ≤20 cigarettes/day), current >20 cigarettes/day), history of diabetes (yes or no), family history of prostate cancer (yes or no), PSA testing (yes, no, unknown), intake of tomato sauce, alpha-linolenic acid and total energy intake (all continuous). Other covariates considered for adjustment but not kept in the final models were intake of calcium, alcohol, processed meat supplemental vitamin E use and multivitamin use. For participants with missing data (generally less than 5%), an indicator variable was included in the models. To minimize the possible effect of change in coffee consumption due to undiagnosed disease, we excluded deaths that occurred during the first two years of follow-up from our analysis.

In further analysis, we stratified by PSA screening history to examine whether results were influenced by differences in screening behavior according to coffee consumption patterns. We also investigated the role of caffeine vs. other components of coffee by estimating the hazard ratios for regular and decaffeinated coffee separately.

Since smoking is a risk factor for fatal prostate cancer and also often linked to increased coffee consumption, we conducted additional analysis restricted the analysis to never smokers or those who had quit for at least 10 years to fully control for the smoking effect. All analyses were conducted on SAS software, version 9.1. Statistical tests were two-sided and p-values of less 0.05 were considered to be statistically significant.

Results

Over 11 years of follow-up (median, 10.5 years) 23,335 cases of prostate cancer were ascertained, including 2,927 advanced and 917 fatal cases. Approximately 9% of the participants reported drinking no coffee and 4% reported drinking six or more cups per day (Table 1). Compared to men who did not drink coffee, men who drank the most coffee were more likely to be current smokers, less likely to be physically active, and less likely to report a history of PSA testing at baseline. About two thirds of coffee drinkers reported drinking mostly caffeinated coffee.

In the multivariate models, we observed no association between coffee consumption and overall prostate cancer (HR: 0.94, 95%CI: 0.86–1.02, p-trend=0.08).

There was no significant association between coffee consumption and advanced prostate cancer (HR: 1.13, 95% CI: 0.91–1.40, p-trend=0.62) or fatal prostate cancer (HR: 0.79, 95% CI: 0.53–1.17, p-trend=0.20), comparing those who drank more than six cups per day to non-drinkers (Table 2). The HR was 0.77 (0.59–1.02) for 4 or more cups vs. none. We conducted a sensitivity analysis using low coffee drinkers (1 or less cups per day) as the referent group. The HR and 95% CI comparing men who consumed ≤ 1cup/day to ≥ 6 cups/day were 0.92 (0.85–0.99) for total prostate cancer and 0.90 (0.63–1.29) for fatal prostate cancer.

When associations were examined stratified by recent PSA screening (provided by 69% of the cohort), similar results were observed for men with and without PSA test. We combined the two top categories (4–5 cups and 6 or more cups per day) for sufficient numbers. The HR for total prostate cancer, comparing those who drank 4 or more cups per day to nondrinkers were 1.01 (95% CI: 0.93–1.09) for men who had a prior PSA test and 1.01 (95% CI: 0.85–1.19) for those who did not. For fatal prostate cancer, the HR (4 or more cups per day vs. none) was 0.78 (95% CI: 0.50–1.23) for those with a prior PSA test and 0.94 (95% CI: 0.47–1.88) for those without a prior PSA.

Since current cigarette smoking was significantly associated with fatal prostate cancer, and highest among men who drank the most coffee, we restricted the analysis to non-smokers (never smokers and those who quit more than ten years earlier) to fully adjust for its effects. We chose this categorization based on evidence that former smokers who have quit for at least 10 years have prostate cancer mortality risk similar to those who never smoked (13). With the effects of smoking fully controlled in these models, the age- and multivariate-adjusted HR, particularly for fatal prostate cancer, were quite similar but the associations remained nonsignificant for overall, advanced and fatal prostate cancer (Table 3).

We also evaluated the association for regular (caffeinated) vs. decaffeinated coffee separately and saw no differences in associations in the two groups. There was also no statistically significant association between total caffeine intake and risk of overall, advanced or fatal prostate cancer (data not shown).

Discussion

In this large prospective cohort study, we found no statistically significant association between coffee consumption and the risk of overall prostate cancer, advanced prostate cancer or fatal prostate cancer. The associations remained nonsignificant even after we restricted the analysis to non-smokers. The results were similar in those who reported a recent PSA screening and those who did not.

Coffee consumption was inversely associated with total prostate cancer in the age-adjusted models but not in the multivariate-adjusted models. Differential PSA screening in men consuming the most coffee compared to non-drinkers could explain this as the percentage of men reporting PSA testing at baseline was 44% in nondrinkers vs. 37% in men consuming 6 or more cups of coffee per day. In an analysis stratified by PSA screening history, the age-adjusted hazard ratios were not statistically significant across the strata.

Findings from past studies on coffee consumption and the risk of prostate cancer have been inconsistent with most, though not all studies, reporting null results (9–12). Most of these studies examined the risk for overall prostate cancer. In the post PSA-era, there is large variation in the biological potential of cases and a large number of latent screen-detected cases will not progress to clinical significance even in the absence of treatment (21). Different factors may affect prostate cancer at various stages of progression, therefore, associations may differ by disease stage (6). It is likely that the factors associated with the development of indolent tumors may be different from those associated with tumors that are likely to advance to metastatic stages (22). By focusing solely on total incident cases, the studies may have missed an association that is specific to lethal disease. Studies examining the association with prostate cancer aggressiveness have also reported differing findings (8, 23, 24). A retrospective cohort reported no significant association (24) whereas two other studies reported an inverse association between high grade prostate cancer and coffee consumption (8, 23).

Only a few studies have examined the association of coffee with lethal or fatal prostate cancer (8, 25, 26). Two studies reported no statistically significant associations of coffee consumption and prostate cancer mortality. The Lutheran cohort (n=149 cases) found no association comparing ≥ 5cups vs. < 3cups per day (26). Phillips et al. (25) reported a non-significant hazard ratio comparing ≥ 2 cups to none (n=98 cases). However, these studies had narrow range of coffee intake, small number of cases and adjusted for few potential confounders that did not include smoking (25, 26). In contrast, the Health Professionals' Follow-up Study (HPFS) found a 60% lower risk of lethal prostate cancer among men who

drank six or more cups of coffee per day compared to non drinkers (HR: 0.40 95% CI: 0.22–0.75) (8).

Study differences may explain the discrepancy between our findings and those in HPFS (8). In an effort to compare the findings from these two studies, we conducted an analysis in HPFS limiting to conditions in the NIH-AARP study i.e. baseline at 1996, coffee consumption assessed once at baseline, and follow-up through 2006. Under these conditions, the results in HPFS were not statistically significant, similar to our findings in the NIH-AARP cohort. The hazard ratios (95% CI) were 0.90 (0.78–1.04), p-trend 0.18 for total prostate cancer and 1.22 (0.64–2.33), p-trend 0.98 for fatal prostate cancer, comparing those who drank 4 or more cups per day to non-drinkers. The findings remained non-significant when stratified by PSA or restricted to nonsmokers. These results may well suggest that longer follow-up, as is the case in HPFS, is important in the relationship between coffee and prostate cancer and, the results from the NIH- AARP cohort may not be at odds with the HPFS study findings. It is possible that any potential latent period between exposure and disease might not be represented in the 10-year follow-up.

Our study had some limitations. Coffee consumption was assessed using a single baseline questionnaire. As such, we were unable to account for any dietary changes during follow-up and likely misclassified those who changed their intake during follow-up. Repeated assessment of coffee consumption over the 11 year follow-up period could have reduced random within-person measurement error (27). It is possible that nondifferential measurement error in the assessment of coffee could have biased our estimates towards the null. It is also possible that confounding by poorly measured confounders could have affected our findings masking the true association.

Despite this, our study had several strengths including the prospective design, and large number of cases ascertained over a long follow-up period that allowed us to examine the association by disease stage. We also had information on a variety of potential confounding factors.

In conclusion, our findings indicate no significant association between coffee consumption assessed at baseline, and risk of overall, advanced or fatal prostate cancer in this large prospective cohort. However, we cannot exclude a modest inverse association. Further studies on coffee and prostate cancer in similarly large prospective cohorts with long follow-up time may shed more light on the association.

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Abbreviations

BMI	Body mass index
CI	Confidence interval

FFQ	Food frequency questionnaire
HR	Hazard ratio
NIH	National Institutes of Health
PSA	Prostate Specific Antigen

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Table 1

Characteristics of the NIH-AARP Diet and Health Study population at baseline, 1995/96 by coffee consumption categories

	Categories of daily total coffee intake					
Characteristics	**None (n=25,768)**	**<1 cup (n=44,988)**	**1 cup (n=44,189)**	**2–3 cups (n=122,088)**	**4–5 cups (n=39,076)**	**≥ 6 cups (n=12,282)**
Mean age at baseline, years	61.4	62.1	63.0	62.3	61.3	60.7
Mean BMI at baseline, kg/m^2	27.1	27.2	27.1	27.4	27.5	27.4
Mean BMI at 18, kg/m^2	21.6	21.5	21.5	21.7	21.9	22.1
Mean height, meters	1.8	1.8	1.8	1.8	1.8	1.8
White, non Hispanic, %	90.2	87.6	90.3	94.4	95.9	96.1
Former smokers, quit >10 years ago, %	32.3	42.4	46.1	47.4	42.5	33.5
Former smokers, quit ≤10 years ago, %	6.4	9.4	11.2	13.9	16.9	18.7
Current smokers, %	4.4	5.3	5.9	10.1	18.8	32.3
Physical activity, ≥ 5 times/week, %	25.1	21.7	21.7	20.9	20.9	20.0
History of PSA screening, %	44.0	44.8	45.5	44.8	42.4	36.7
Family history of prostate cancer, %	8.7	8.3	8.1	8.3	8.4	8.4
History of diabetes, %	9.8	10.6	10.7	9.6	9.4	9.3
Dietary intake						
Alcohol, g/1000 kcal	4.4	6.3	7.2	8.3	7.9	6.3
Calcium, mg/1000 kcal	428.1	423.4	406.1	407.7	408.7	408.1
Processed meat, g/1000 kcal	11.4	11.2	11.9	12.0	12.6	13.2
Alpha-linolenic acid, g/1000 kcal	0.7	0.7	0.7	0.7	0.7	0.7
Tomato sauce, g/1000 kcal	10.9	11.7	12.3	12.0	11.4	10.9
Multivitamin use, %	51.7	53.3	51.2	51.7	51.4	50.2
Supplementary vitamin E use, %	69.8	73.2	68.6	66.4	64.6	60.0

Abbreviations: NIH- National Institutes of Health; BMI- body mass index; PSA- prostate specific antigen

Table 2

Hazard ratios and 95% confidence intervals of prostate cancer by categories of coffee consumption in the NIH-AARP Diet and Health Study

	Categories of total coffee intake						
	None	**< 1 cup/day**	**1cup/day**	**2–3 cups/day**	**4–5 cups/day**	**≤6 cups/day**	**p-trend**
Total prostate cancer							
n=23,335	2,136	3,894	3,781	9,835	2,902	787	
Age-adjusted HR	1.00	1.01 (0.96, 1.07)	0.96 (0.91, 1.01)	0.94 (0.89, 0.98)	0.91 (0.86, 0.96)	0.82 (0.76, 0.89)	<0.0001
Multivariate-adjusted HR	1.00	1.03 (0.98, 1.08)	1.00 (0.95, 1.06)	1.00 (0.96, 1.05)	1.00 (0.94, 1.06)	0.94 (0.87, 1.02)	0.08
Fatal prostate cancer							
n=917	87	144	139	400	110	37	
Age-adjusted HR	1.00	0.89 (0.69, 1.17)	0.81 (0.62, 1.06)	0.90 (0.72, 1.14)	0.86 (0.65, 1.14)	1.02 (0.69, 1.49)	0.87
Multivariate-adjusted HR	1.00	0.89 (0.68, 1.16)	0.81 (0.62, 1.06)	0.87 (0.69, 1.11)	0.77 (0.58, 1.03)	0.80 (0.53, 1.18)	0.20
Advanced prostate cancer							
n= 2,927	264	510	440	1,185	401	127	
Age-adjusted HR	1.00	1.09 (0.94, 1.26)	0.93 (0.80, 1.08)	0.92 (0.81, 1.06)	1.01 (0.86,1.17)	1.04(0.84, 1.29)	0.56
Multivariate-adjusted HR	1.00	1.10 (0.95, 1.28)	0.97 (0.83, 1.14)	0.98 (0.86, 1.12)	1.08 (0.92, 1.27)	1.15 (0.92, 1.43)	0.62
Nonadvanced prostate cancer							
n=18,993	1,744	3,168	3,097	8,048	2,325	611	
Age-adjusted HR	1.00	1.01 (0.95, 1.07)	0.96 (0.90, 1.02)	0.94 (0.89, 0.99)	0.89 (0.84, 0.95)	0.78 (0.72, 0.86)	<0.0001
Multivariate-adjusted HR	1.00	1.03 (0.97, 1.09)	1.01 (0.95, 1.07)	1.01 (0.96, 1.07)	0.99 (0.93, 1.06)	0.92 (0.84, 1.01)	0.07

The multivariate models are adjusted for age, race, height, BMI, physical activity, smoking, history of diabetes, family history of prostate cancer, PSA testing, intakes of tomato sauce, alpha-linolenic acid and total energy intake.

Cases with missing stage are included in the total prostate cancer count but not in the subtypes.

Abbreviations: BMI, body mass index; HR, hazard ratio; NIH, National Institutes of Health; PSA, prostate specific antigen.

Table 3

Hazard ratios and 95% confidence intervals of prostate cancer by coffee consumption categories among non-smokers in the NIH-AARP Diet and Health Study

	Categories of total coffee intake					
	None	**< 1 cup/day**	**1cup/day**	**2–3 cups/day**	**≥4 cups/day**	**p-trend**
Total prostate cancer						
n=18,082	1,901	3,272	3,084	7,459	2,366	
Age-adjusted HR	1.00	1.01 (0.95, 1.06)	0.95 (0.90, 1.01)	0.94 (0.89, 0.99)	0.94 (0.88, 1.00)	0.001
Multivariate-adjusted HR	1.00	1.01 (0.95, 1.07)	0.98 (0.92, 1.04)	0.97 (0.92, 1.02)	0.98 (0.92, 1.04)	0.16
Fatal prostate cancer						
n=611	68	112	107	252	72	
Age-adjusted HR	1.00	0.93 (0.69, 1.26)	0.85 (0.63, 1.15)	0.84 (0.64, 1.10)	0.80 (0.57, 1.11)	0.17
Multivariate-adjusted HR	1.00	0.94 (0.70, 1.27)	0.87 (0.64, 1.19)	0.86 (0.66, 1.13)	0.81 (0.58, 1.14)	0.19
Advanced prostate cancer						
n=2,187	230	419	352	875	311	
Age-adjusted HR	1.00	1.08 (0.92, 1.27)	0.93 (0.79, 1.10)	0.93 (0.80, 1.07)	1.02 (0.86, 1.21)	0.38
Multivariate-adjusted HR	1.00	1.09 (0.93, 1.28)	0.97 (0.82, 1.14)	0.96 (0.83, 1.11)	1.07 (0.90, 1.27)	0.82
Nonadvanced prostate cancer						
n=14,888	1,557	2,674	2,553	6,171	1,933	
Age-adjusted HR	1.00	1.00 (0.94, 1.02)	0.96 (0.90, 1.00)	0.95 (0.90, 1.00)	0.94 (0.88, 1.00)	0.004
Multivariate-adjusted HR	1.00	1.00 (0.94, 1.07)	0.99 (0.93, 1.05)	0.98 (0.93, 1.03)	0.98 (0.92, 1.05)	0.28

The multivariate models are adjusted for age, race, height, BMI, physical activity, history of diabetes, family history of prostate cancer, PSA testing, intakes of tomato sauce, alpha-linolenic acid and total energy intake.

Cases with missing stage are included in the total prostate cancer count but not in the subtypes.

Abbreviations: BMI, body mass index; HR, hazard ratio; NIH, National Institutes of Health; PSA, prostate specific antigen.