

Coffee Consumption and Prostate Cancer Risk and Progression in the Health Professionals Follow-up Study

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Background Coffee contains many biologically active compounds, including caffeine and phenolic acids, that have potent antioxidant activity and can affect glucose metabolism and sex hormone levels. Because of these biological activities, coffee may be associated with a reduced risk of prostate cancer.

Methods We conducted a prospective analysis of 47 911 men in the Health Professionals Follow-up Study who reported intake of regular and decaffeinated coffee in 1986 and every 4 years thereafter. From 1986 to 2006, 5035 patients with prostate cancer were identified, including 642 patients with lethal prostate cancers, defined as fatal or metastatic. We used Cox proportional hazards models to assess the association between coffee and prostate cancer, adjusting for potential confounding by smoking, obesity, and other variables. All *P* values were from two-sided tests.

Results The average intake of coffee in 1986 was 1.9 cups per day. Men who consumed six or more cups per day had a lower adjusted relative risk for overall prostate cancer compared with nondrinkers (RR = 0.82, 95% confidence interval [CI] = 0.68 to 0.98, $P_{\text{trend}} = .10$). The association was stronger for lethal prostate cancer (consumers of more than six cups of coffee per day: RR = 0.40, 95% CI = 0.22 to 0.75, $P_{\text{trend}} = .03$). Coffee consumption was not associated with the risk of nonadvanced or low-grade cancers and was only weakly inversely associated with high-grade cancer. The inverse association with lethal cancer was similar for regular and decaffeinated coffee (each one cup per day increment: RR = 0.94, 95% CI = 0.88 to 1.01, $P = .08$ for regular coffee and RR = 0.91, 95% CI = 0.83 to 1.00, $P = .05$ for decaffeinated coffee). The age-adjusted incidence rates for men who had the highest (≥ 6 cups per day) and lowest (no coffee) coffee consumption were 425 and 519 total prostate cancers, respectively, per 100 000 person-years and 34 and 79 lethal prostate cancers, respectively, per 100 000 person-years.

Conclusions We observed a strong inverse association between coffee consumption and risk of lethal prostate cancer. The association appears to be related to non-caffeine components of coffee.

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Coffee contains diverse biologically active compounds that include caffeine, minerals, and phytochemicals. Long-term coffee drinking has been associated with improved glucose metabolism and insulin secretion in observational and animal studies (1). Coffee is also a potent antioxidant (2–4) and may be associated with sex hormone levels (5–7).

Coffee consumption has been consistently associated with a reduced risk of type 2 diabetes (8), and its effects on insulin, sex hormones, and antioxidants may also be relevant to prostate cancer. We hypothesized that coffee may be associated with lower risk of more advanced prostate cancers because the associations of insulin, antioxidants, and androgens with incidence of prostate cancer are stronger for advanced disease than for overall disease (9–15).

Epidemiological studies of coffee consumption and prostate cancer have generally reported null results (16–30), although most lacked a wide range of coffee intakes and a large number of case subjects and none specifically examined advanced disease. The two studies of coffee consumption and prostate cancer mortality (31,32) found no statistically significant associations, but these were limited by a narrow range of intake, small number of cancer deaths, and inadequate adjustment for potential confounding.

We investigated the relationship between coffee intake and risk of overall prostate cancer and of aggressive disease, defined as lethal, advanced, or high-grade cancer, in the Health Professionals Follow-up Study.

Methods

The Health Professionals Follow-up Study is a prospective cohort study of 51 529 male health professionals in the United States aged 40–75 years at baseline in 1986. The men are followed through biennial questionnaires to update information on lifestyle and health outcomes, and usual diet has been assessed every 4 years.

Men who completed the baseline food frequency questionnaire (FFQ) in 1986 form the study population for this analysis ($N = 49\,911$). We excluded men who had an implausible energy intake (<800 or >4200 kcal/day) or who left more than 70 food items blank on the baseline FFQ. We also excluded men who reported a diagnosis of cancer (except nonmelanoma skin cancer) before baseline ($N = 2000$). This left a total of 47 911 men who were followed prospectively for cancer incidence until 2006 and for metastases and mortality outcomes until 2008. The Health Professionals Follow-up Study is approved by the Human Subjects Committee at the Harvard School of Public Health.

Assessment of Coffee Intake

Updated dietary data, including coffee consumption, was available from FFQs, which reported on intake of over 130 food items at baseline in 1986, and again in 1990, 1994, 1998, and 2002. Participants were asked how frequently they had consumed a specified portion size of each item over the previous year, with nine possible responses ranging from “never or less than once a month” to “six or more times per day.” The FFQ included questions concerning cups of decaffeinated and regular coffee intake. A validation study in this cohort found a high correlation ($r = 0.93$) between participants’ reports of coffee intake on the FFQ compared with two week-long diet records (33).

Ascertainment and Classification of Subjects Who Developed Prostate Cancer

Prostate cancer diagnoses were initially identified by self-reports from the participants or their next of kin on the biennial questionnaires and then confirmed by review of medical records and pathology reports. Deaths in the cohort were ascertained through reports from family members and searches of the National Death Index. Underlying cause of death was assigned by an endpoints committee based on all available data including medical history, medical records, registry information, and death certificates. Approximately 90% of prostate cancer patients were documented by medical records; the remaining 10% of men with prostate cancer, based on self-reports or death certificates, were included because the reporting of prostate cancer was highly accurate ($>98\%$) among men with available medical records. We followed men with prostate cancer starting in 2000 with an additional prostate cancer-specific questionnaire separate from the regular Health Professionals Follow-up Study questionnaire every year to ascertain disease progression and diagnosis of metastases.

We studied total prostate cancer incidence excluding stage T1a cancers, which are discovered incidentally during treatment for benign prostatic hypertrophy. Because of the considerable heterogeneity in the biological potential of prostate cancer, we also examined the data for men with advanced, lethal, or nonadvanced cancers separately to distinguish those patients in whom the can-

CONTEXT AND CAVEATS

Prior knowledge

Previous epidemiological studies have generally found no association between coffee consumption and risk of prostate cancer, but all such studies had limitations and none focused on advanced disease.

Study design

The association between coffee intake and risk of prostate cancer was prospectively analyzed among 47 911 men of the Health Professionals Follow-Up Study, who had repeatedly provided nutritional data since 1986. Cancer incidence was followed until 2006 and metastases and mortality until 2008. Relative risks were computed and adjusted for age, smoking, obesity, and other variables.

Contribution

Men who drank six or more cups of coffee per day had a slightly lower adjusted relative risk of prostate cancer and a substantially lower adjusted relative risk of lethal prostate cancer compared with nondrinkers. Both caffeinated and decaffeinated coffee consumption were associated with similarly reduced risks.

Implications

There may be biologically active compounds in coffee that protect against risk of lethal prostate cancer.

Limitations

The results depend on self-reported nutritional data and correction for multiple possible confounders. Coffee consumption was not found to be associated with risk of lower grade prostate cancers.

From the Editors

cer was likely to progress clinically. Advanced cancers were those that had spread beyond the prostate, including to the seminal vesicle, lymph nodes, or bone. This category included men with stage T3b, T4, N1, or M1 prostate cancer at diagnosis, men who developed lymph node or distant metastases, and men who died of prostate cancer before the end of follow-up. Lethal cancers, a subset of advanced cancers, were those that caused death or metastasis to bone before the end of follow-up. Nonadvanced cancers were stage T1 or T2 and N0 and M0 at diagnosis and did not progress to lymph node or distant metastases or death during the follow-up period. (Some cancers that were diagnosed near the end of the follow-up period will be misclassified as nonadvanced because they had less time to progress before the end of follow-up). Cancers were also categorized as high grade (Gleason sum at diagnosis 8–10), grade 7, or low grade (Gleason sum 2–6) at diagnosis based on prostatectomy or biopsy pathology reports; Gleason grade was not available for all men with prostate cancer, particularly for those who were diagnosed earlier in the follow-up period.

Statistical Analysis

Each participant contributed person-time from the date on which he returned the baseline questionnaire in 1986 until prostate cancer diagnosis, death, or the end of the study period, January 31, 2006. Participants were followed for prostate cancer incidence until January 31, 2006, and for death and metastases until January

31, 2008. Participants' data were divided according to levels of total (regular and decaffeinated) coffee intake, and relative risks of prostate cancer were calculated as the incidence rate in a given category of intake divided by the rate in the lowest category, adjusted for age and calendar time.

Because coffee intake may affect carcinogenesis over an extended period, we used the cumulative average intake of coffee to represent long-term dietary intake as our primary measure of exposure. That is, the coffee intake reported by participants in 1986 was used to compute exposure for the 1986–1990 follow-up period, the average of the intakes reported in 1986 and 1990 was used for the 1990–1994 follow-up period, the average of intakes reported in 1986, 1990, and 1994 was used for the 1994–1998 follow-up period, and so on. In a secondary analysis, we used baseline (1986) coffee intake only. In addition, we used our repeated measures to analyze the effect of latency time (time from exposure to cancer diagnosis) by relating each measure of coffee intake to prostate cancer incidence during specific time periods: 0–4, 4–8, 8–12, and 12–16 years after exposure. Finally, to assess the potential for symptoms of subclinical advanced disease to affect coffee intake (reverse causation), we conducted a secondary analysis using cumulative average intake with a lag of 4 years to avoid using data on coffee consumption from FFQs completed immediately before diagnosis.

We used Cox proportional hazards regression to adjust for potential confounding by prostate cancer risk factors previously identified in this cohort and in other studies. Scaled Schoenfeld residuals were used to test the proportional hazards assumption. Multivariable models were adjusted for race (White, African American, Asian American, other), height (quartiles), body mass index at age 21 (<20, 20 to <22.5, 22.5 to <25, ≥ 25 kg/m²), current body mass index (<21, 21 to <23, 23 to <25, 25 to <27.5, 27.5 to <30, ≥ 30 kg/m²), vigorous physical activity (quintiles, metabolic equivalents-hours/week), smoking (never, former quit >10 years ago, former quit <10 years ago, current), diabetes (type I or II, yes or no), family history of prostate cancer in father or brother (yes or no), multivitamin use (yes or no), history of prostate-specific antigen (PSA) testing (yes or no, lagged by one period to avoid counting diagnostic PSA tests as screening; collected from 1994 onwards), and intakes of processed meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, alcohol intake (all quintiles), and energy intake (continuous). All covariates except race, height, and body mass index at age 21 were updated in each questionnaire cycle. To test for a linear trend across categories of intake, we modeled coffee intake as a continuous variable using the median intake for each category.

Because we found associations for total coffee intake, we repeated our analyses for regular and decaffeinated coffee separately, and for caffeine intake to see if the observed associations were related to caffeine or other components of coffee. To investigate possible confounding due to differences in PSA testing, we stratified by time period to determine whether the association between coffee and prostate cancer risk differed in the pre-PSA (1986–1994) and PSA screening eras (1994–2006). All *P* values were two-sided, with a *P* value less than .05 considered to be statistically significant. Analyses were performed using SAS version 9.1 (SAS Institute, Inc; Cary, NC).

Results

During 20 years (816 130 person-years) of follow-up, 5035 of 47 911 men were confirmed to have developed prostate cancer. Of these cancers, 642 were lethal, 896 were advanced (642 lethal plus 254 additional extraprostatic cancers), and 3221 were nonadvanced prostate cancers. Two-thirds of all cohort participants consumed at least one cup of coffee per day in 1986, and 5% reported drinking six or more cups daily (Table 1). Men who consumed the most coffee were more likely to be ever-smokers and were less likely to engage in vigorous physical activity (Table 1). Frequency of PSA testing was similar among high and low coffee drinkers, whereas men in the middle categories reported somewhat more testing. High coffee consumption was associated with higher intakes of energy, alcohol, and processed meat, and slightly lower intake of calcium.

We observed a weak inverse association between total coffee intake and incidence of prostate cancer (Table 2). Men who consumed six or more cups per day had an 18% lower risk of prostate cancer compared with men who did not drink coffee (relative risk [RR] = 0.82, 95% confidence interval [CI] = 0.68 to 0.98, $P_{\text{linear trend}} = .10$). The age-adjusted incidence rates of prostate cancer for the highest (≥ 6 cups per day) and lowest (no coffee) coffee categories were 425 and 529 cancers per 100 000 person-years, respectively. The data suggested an inverse association between coffee intake and risk of high-grade cancers, although the trends were not statistically significant. Coffee was not associated with low-grade cancer.

The strongest associations were for lethal and advanced prostate cancer (men in the highest intake category vs nondrinkers: RR = 0.40, 95% CI = 0.22 to 0.75, $P_{\text{trend}} = .03$ for lethal cancer; RR = 0.47, 95% CI = 0.28 to 0.77, $P_{\text{trend}} = .004$ for advanced cancer). The age-adjusted incidence rates of lethal prostate cancer for the highest and lowest intake categories were 34 and 79 per 100 000 person-years, respectively. Coffee consumption was not associated with risk of nonadvanced cancers that never progressed beyond the prostate.

For comparison with other studies without repeated measures of diet, we repeated the analyses using baseline rather than cumulative coffee intake. With baseline intake the associations of coffee consumption with lethal and advanced cancers remained statistically significant but were somewhat attenuated (the highest vs lowest coffee consumers in 1986: RR = 0.50, 95% CI = 0.30 to 0.84, $P_{\text{trend}} = .05$ for lethal prostate cancer; RR = 0.54, 95% CI = 0.36 to 0.83, $P_{\text{trend}} = .03$ for advanced disease).

To examine whether urinary symptoms affected coffee intake before diagnosis (reverse causation), we looked cross-sectionally at coffee and lower urinary tract symptoms in 1998. We found that coffee intake did not differ in men with and without urinary symptoms. Men were asked to report the frequency of seven urinary symptoms, and these were combined to create four categories of lower urinary tract symptoms scores that ranged from no or low levels of symptoms to severe levels of symptoms (34). Mean coffee intake in the lowest symptom group was 1.59 cups per day (SD = 1.53) and mean coffee intake in the severe symptoms group was 1.57 (SD = 1.58, *P* for difference in means = .73). There was also no statistically significant trend in total coffee intake across the four symptom groups ($P_{\text{linear trend}} = .20$).

Table 1. Age-adjusted characteristics of the Health Professionals Follow-up Study population at baseline in 1986, by coffee consumption*

Characteristic	Category of total coffee intake				
	None (n = 7890)	<1 cup per day (n = 9533)	1–3 cups per day (n = 21 261)	4–5 cups per day (n = 6735)	≥6 cups day (n = 2492)
Mean age, y	52	55	55	54	53
White race, %	95	94	96	98	98
Mean BMI, kg/m ²	25	25	26	26	26
Mean BMI at age 21, kg/m ²	23	23	23	23	23
Mean height, inches	70	70	70	70	70
Former smoker, quit >10 y ago, %	20	28	32	34	31
Former smoker, quit ≤10 y ago, %	6	10	14	17	17
Current smokers, %	4	6	10	16	25
Vigorous activity (% highest quintile)	17	17	15	15	11
Diabetes, %	3	3	3	3	3
Family history of prostate cancer, %	13	11	12	12	12
PSA test, 1994, %	35	39	38	38	33
PSA test, 2004, %	60	64	66	66	58
Mean dietary intakes					
Energy, kcal/d	1960	1895	1990	2069	2159
Alcohol, g/d	6	9	13	14	15
Calcium, mg/d	973	931	866	881	873
Alpha-linolenic acid, g/d	1.1	1.1	1.1	1.1	1.1
Supplemental vitamin E, mg/day	41.5	45.1	36.1	33.3	33.0
Multivitamin use, %	42	44	41	40	38
Processed meat, servings per week	2.1	2.1	2.6	2.9	3.4
Tomato sauce, servings per week	0.9	0.9	0.9	0.9	0.9
Total coffee, servings per day	0.0	0.5	1.9	4.2	6.3
Regular coffee, servings per day	0.0	0.2	1.3	2.9	4.2
Decaffeinated coffee, servings per day	0.0	0.2	0.6	1.3	2.0

* All variables (except age) are standardized to the age distribution of the cohort at baseline. BMI = body mass index; PSA = prostate-specific antigen.

In addition, we conducted several other analyses to assess possible reverse causation. Results for lethal and advanced cancers were similar when men with distant metastases or unknown metastasis status at diagnosis were excluded (data not shown). We also studied the subset of men with advanced cancers that were localized at diagnosis (stage <T3b) and spread only later (n = 294), because these cancers were less likely to be symptomatic before diagnosis than cancers that were diagnosed at an advanced stage. The risk was similar to that seen for all men with advanced cancers (RR = 0.20, 95% CI = 0.06 to 0.65, $P_{\text{trend}} = .02$). We also examined coffee intake with a 4-year lag period between exposure and outcome to avoid using the FFQ data that were collected immediately before diagnosis. The associations with lethal and advanced cancers were somewhat attenuated but remained statistically significant using this exposure measure (RR = 0.58, 95% CI = 0.33 to 1.01, $P_{\text{trend}} = .02$ for lethal cancer; RR = 0.59, 95% CI = 0.37 to 0.94, $P_{\text{trend}} = .008$ for advanced cancer).

To examine whether confounding by PSA testing might explain our findings, we stratified by time period and evaluated the pre-PSA and PSA eras separately. The association of coffee and advanced disease was similar in both time periods (for 1986–1994, RR of advanced cancer for the highest vs lowest categories of intake = 0.41 [95% CI = 0.20 to 0.85, $P_{\text{trend}} = .06$]; for 1994–2006, RR = 0.53 [95% CI = 0.26 to 1.05, $P_{\text{trend}} = .03$]). We also examined a subcohort of men who reported PSA testing in 1994, with follow-up from 1994 until 2006. We observed inverse associations between coffee intake and risk of lethal and advanced cancers in

this subcohort that were of similar magnitude to those in the main analyses, but the estimates were not statistically significant, perhaps due to limited power, given the small numbers of lethal and advanced cancers in this highly screened group (in the screened subcohort, RR for advanced cancer [n = 199] = 0.39 [95% CI = 0.11 to 1.34, $P_{\text{trend}} = .29$] for the highest vs lowest category of intake). Coffee consumption was not associated with nonadvanced cancer in this subcohort.

To investigate the role of caffeine vs other components of coffee, we studied regular and decaffeinated coffee separately and found similar associations for both with lethal and advanced cancers (Tables 3 and 4). Compared with men who drank no coffee at all (regular or decaf), men who drank six or more cups per day of regular coffee had a lower risk for advanced cancer, adjusting for decaffeinated coffee intake as a continuous variable (RR = 0.69, 95% CI = 0.38 to 1.27, $P_{\text{trend}} = .01$). Compared with nondrinkers, men who drank four or more cups per day of decaffeinated coffee had a lower risk for advanced cancer, adjusting for regular coffee intake as a continuous variable (RR = 0.67, 95% CI = 0.43 to 1.05, $P_{\text{trend}} = .02$). To compare these associations quantitatively, we included caffeinated and decaffeinated coffee as continuous variables in the same model. For advanced cancer, these relative risks were not statistically significantly different from one another (each one cup per day increment: RR = 0.94, 95% CI = 0.89 to 0.99, $P = .03$ for regular coffee and RR = 0.92, 95% CI = 0.85 to 1.00, $P = .04$ for decaffeinated coffee; P for difference in coefficients = .68). Similar associations for regular and decaffeinated coffee were seen

Table 2. Relative risk (RR) with 95% confidence interval (95% CI) of prostate cancer by category of total coffee intake, 1986–2006*

Risk of prostate cancer	Category of coffee intake					<i>P</i> _{trend}
	None	<1 cup/d	1–3 cups/d	4–5 cups/d	≥6 cups/d	
All prostate cancers, No.	587	1139	2438	719	152	
Age-adjusted RR (95% CI)	1.00	0.96 (0.87 to 1.06)	0.97 (0.88 to 1.06)	0.95 (0.85 to 1.06)	0.81 (0.67 to 0.96)	.08
Fully adjusted RR (95% CI)	1.00	0.94 (0.85 to 1.05)	0.94 (0.86 to 1.04)	0.93 (0.83 to 1.04)	0.82 (0.68 to 0.98)	.10
Lethal prostate cancers†, No.	89	150	298	93	12	
Age-adjusted RR (95% CI)	1.00	0.76 (0.58 to 0.99)	0.73 (0.58 to 0.93)	0.83 (0.62 to 1.11)	0.43 (0.24 to 0.80)	.08
Fully adjusted RR (95% CI)	1.00	0.76 (0.58 to 1.00)	0.71 (0.55 to 0.92)	0.76 (0.56 to 1.04)	0.40 (0.22 to 0.75)	.03
Advanced prostate cancers†, No.	122	211	422	122	19	
Age-adjusted RR (95% CI)	1.00	0.81 (0.65 to 1.02)	0.78 (0.63 to 0.95)	0.79 (0.61 to 1.01)	0.49 (0.30 to 0.80)	.01
Fully adjusted RR (95% CI)	1.00	0.81 (0.64 to 1.02)	0.75 (0.60 to 0.93)	0.73 (0.56 to 0.95)	0.47 (0.28 to 0.77)	.004
Nonadvanced prostate cancers†, No.	353	729	1554	483	102	
Age-adjusted RR (95% CI)	1.00	1.04 (0.91 to 1.18)	1.04 (0.92 to 1.16)	1.04 (0.91 to 1.20)	0.88 (0.71 to 1.10)	.60
Fully adjusted RR(95% CI)	1.00	1.01 (0.88 to 1.15)	0.99 (0.87 to 1.12)	1.02 (0.88 to 1.18)	0.93 (0.74 to 1.16)	.77
Grade 8–10 cancers, No.	61	111	255	78	11	
Age-adjusted RR (95% CI)	1.00	0.86 (0.63 to 1.18)	0.93 (0.70 to 1.23)	0.96 (0.69 to 1.35)	0.57 (0.30 to 1.09)	.58
Fully adjusted RR (95% CI)	1.00	0.84 (0.61 to 1.16)	0.87 (0.65 to 1.18)	0.88 (0.61 to 1.26)	0.53 (0.27 to 1.02)	.29
Grade 7 cancers, No.	174	295	641	226	41	
Age-adjusted RR (95% CI)	1.00	0.86 (0.72 to 1.04)	0.88 (0.74 to 1.04)	0.98 (0.80 to 1.20)	0.69 (0.49 to 0.97)	.58
Fully adjusted RR (95% CI)	1.00	0.85 (0.70 to 1.04)	0.85 (0.71 to 1.02)	0.94 (0.76 to 1.16)	0.69 (0.49 to 0.99)	.50
Grade 2–6 cancers, No.	232	489	1045	298	70	
Age-adjusted RR (95% CI)	1.00	1.08 (0.92 to 1.26)	1.07 (0.93 to 1.24)	0.99 (0.83 to 1.18)	0.94 (0.72 to 1.23)	.34
Fully adjusted RR (95% CI)	1.00	1.02 (0.87 to 1.20)	1.01 (0.87 to 1.18)	0.96 (0.80 to 1.15)	1.00 (0.75 to 1.31)	.53

* All relative risks are from an age-adjusted model adjusted for age in months and calendar time. The multivariable model was additionally adjusted for: race (White, African American, Asian American, Other), height (quartiles), BMI at age 21 (<20, 20 to <22.5, 22.5 to <25, ≥25), current BMI (<21, 21 to <23, 23 to <25, 25 to <27.5, 27.5 to <30, ≥30 kg/m²), vigorous physical activity (quintiles), smoking (never, former quit >10 years ago, former quit <10 years ago, current), diabetes (type I or II, yes/no), family history of prostate cancer in father or brother (yes/no), multivitamin use (yes/no), intakes of processed meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, alcohol intake (all quintiles), and energy intake (continuous), and history of PSA testing (yes/no, lagged by one period to avoid counting diagnostic PSA tests as screening; collected from 1994 onwards). All *P* values were from two-sided tests. BMI = body mass index; PSA, prostate-specific antigen.

† Lethal prostate cancer: Prostate cancer death or bone metastases at diagnosis or during follow-up. Advanced: Lethal, or stage T3b, T4, N1, or M1 at diagnosis, or spread to lymph nodes or other metastases during follow-up. Nonadvanced: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

for lethal cancer (for each one cup per day increment, RR = 0.94, 95% CI = 0.88 to 1.01, *P* = .08 for regular coffee and RR = 0.91, 95% CI = 0.83 to 1.00, *P* = .05 for decaffeinated coffee).

To further explore whether the association with lethal and advanced disease was related to caffeine or to other components of coffee, we studied total caffeine intake from all sources. Caffeine intake was inversely associated with lethal and advanced cancers (the highest vs lowest quintile: RR = 0.77, 95% CI = 0.61 to 0.96, *P*_{trend} = .01 for advanced). However, when coffee and caffeine were included in the model together, coffee intake continued to be associated with lethal or advanced disease, whereas caffeine no longer had a statistically significant association with lethal or advanced disease (RR = 0.86, 95% CI = 0.65 to 1.13, *P*_{trend} = .23 for advanced).

We used the repeated measures of coffee intake over time to study the effect of latency time by relating each measure of coffee intake to prostate cancer incidence during specific time intervals after exposure. In this analysis, coffee intake was most strongly inversely associated with risk of advanced prostate cancer for the shorter latency periods, 0–4 and 4–8 years after exposure, and weaker for 8- to 12-year and 12- to 16-year lags (Table 5). Coffee consumption was not associated with nonadvanced cancer for any latency period.

Discussion

In this large prospective study, coffee intake was weakly inversely associated with overall risk of prostate cancer, but it was associated with statistically significantly lower risk of lethal and advanced prostate cancers, with those who drank the most coffee having less than half the risk of these outcomes as nondrinkers. Coffee was not associated with nonadvanced or low-grade cancer and only weakly inversely associated with high-grade cancers. Inverse associations with lethal and advanced disease were similar for regular and decaffeinated coffee. The associations were stronger for more recent coffee exposure, suggesting possible effects later in the development of advanced prostate cancers.

The characteristics of heavy coffee drinkers make it unlikely that confounding is a major explanation for these findings because coffee drinkers were more likely to smoke and less likely to engage in vigorous exercise, behaviors which may increase advanced prostate cancer risk. Therefore, confounding by smoking and other lifestyle factors would bias the associations toward the null, rather than explaining the inverse associations for coffee that we observed. In addition, PSA testing was similar for high coffee consumers and nonconsumers, and results were similar in pre-PSA and PSA eras. Thus, PSA screening is an unlikely explanation for these associations.

Table 3. Relative risk (RR) and 95% confidence interval (95% CI) of prostate cancer by category of regular coffee intake*

Risk of prostate cancer	Category of regular (with caffeine) coffee intake					P _{trend}	No regular, some decaf
	No coffee at all†	<1 cup per day	1–3 cups per day	4–5 cups per day	≥6 cups per day		
Lethal prostate cancer‡, No.	89	207	209	52	6		79
Fully adjusted RR (95% CI)*	1.00	0.81 (0.61 to 1.07)	0.71 (0.54 to 0.93)	0.77 (0.53 to 1.10)	0.46 (0.20 to 1.08)	.07	0.72 (0.51 to 1.01)
Advanced prostate cancer‡, No.	122	298	293	65	12		106
Fully adjusted RR (95% CI)*	1.00	0.86 (0.69 to 1.09)	0.74 (0.59 to 0.93)	0.70 (0.51 to 0.95)	0.69 (0.38 to 1.27)	.01	0.75 (0.56 to 1.00)
Nonadvanced prostate cancer‡, No.	353	1042	1164	270	43		349
Fully adjusted RR (95% CI)*	1.00	0.98 (0.86 to 1.12)	0.99 (0.87 to 1.12)	1.00 (0.84 to 1.18)	0.93 (0.67 to 1.29)	.97	1.10 (0.93 to 1.29)

* All relative risks are from a multivariable model adjusted for: age in months, calendar time, race (White, African American, Asian American, Other), height (quartiles), BMI at age 21 (four categories), current BMI (six categories), vigorous physical activity (quintiles), smoking (never, former quit >10 years ago, former quit <10 years ago, current), diabetes (type I or II, yes/no), family history of prostate cancer in father or brother (yes/no), multivitamin use (yes/no), intakes of processed meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, alcohol intake (all quintiles), energy intake (continuous), and history of prostate-specific antigen testing. Models for regular coffee are also adjusted for decaffeinated coffee intake (continuous). All P values are from two-sided tests. BMI = body mass index.

† Reference group is men who drink no regular or decaffeinated coffee.

‡ Lethal prostate cancer: Prostate cancer death or bone metastases at diagnosis or during follow-up. Advanced: Lethal, or stage T3b, T4, N1, or M1 at diagnosis, or spread to lymph nodes or other metastases during follow-up. Nonadvanced: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

Reverse causation is a possible explanation for these findings. Men with undiagnosed prostate cancer might decrease their consumption of coffee due to urinary symptoms. However prostate cancer often produces no urinary symptoms, because most tumors arise in the peripheral zone of the gland (35). Indeed, we found no association between lower urinary tract symptoms and coffee intake. Moreover, in subanalyses to explore reverse causation, the association between coffee and risk of advanced or lethal prostate cancer remained statistically significant. Thus, reverse causation does not appear to explain the association.

Previous studies of coffee and prostate cancer have generally not reported the striking inverse associations that we observed (16–32). However, all but two studies reported findings only for overall prostate cancer, potentially overlooking inverse associations with advanced disease. Several studies were limited by a narrow range in coffee intakes, small numbers of case subjects, and lack of adjustment for smoking; confounding by smoking could obscure an inverse association because smoking is associated with coffee consumption in many populations and is also associated with prostate cancer-specific mortality (36).

Prostate cancer mortality, an outcome more comparable to our lethal disease, was examined in two cohorts (31,32). Both adjusted only for age as a potential confounder. The Seventh-day Adventists cohort (31) found a relative risk of 0.70 for men drinking two or more cups per day compared with nondrinkers, based on 93 cancer deaths. Hsing et al. (32) found no association between coffee and prostate cancer death in the Lutheran Brotherhood cohort, based on 149 deaths (≥5 cups per day vs reference <3 cups daily: RR = 1.0, 95% CI = 0.6 to 1.6). The results from both studies are compatible with our findings for lethal prostate cancer, given the wide confidence intervals, differing categorizations of intake, and lack of control for smoking. Smoking is likely less of an issue in the Seventh-day Adventists cohort (a population with very low smoking rates), which observed results closer to ours. However, the range of exposures was low in this cohort, with only 5% of men consuming more than two cups of coffee daily.

Three prospective cohort studies found no statistically significant associations between coffee intake and prostate cancer incidence. Two reports from a cohort of 8000 Japanese men in Hawaii found no association, based on 174 incident cancers (16,17). Another Hawaiian cohort (18) also found no association, though coffee intake was low, such that the highest category was greater than 2.5 cups per day. A Norwegian cohort (19) that included 260 men with prostate cancer found a statistically nonsignificant relative risk of 0.74 for men who consumed seven or more cups per day compared with men who consumed two or fewer cups. The Norwegian study (19) was the only prospective cohort to adjust for smoking.

Five population-based and two hospital-based case-control studies found no association of coffee intake and overall prostate cancer incidence (20–24,29,30), whereas two hospital-based studies (25,26) found increased risks of prostate cancer with higher coffee intake. A small retrospective cohort study in Canada (27) and a prospective case-control study in Sweden (28) found positive associations between coffee and prostate cancer, but these were not statistically significant and the confidence intervals were wide in both studies. None of the studies that found positive associations

Table 4. Relative risk (RR) and 95% confidence interval (CI) of prostate cancer by category of decaffeinated coffee intake*

	No coffee at all†	Category of decaffeinated coffee intake			P _{trend}	No decaf, some regular
		<1 cup/d	1–3 cups/d	≥4 cups/d		
Lethal prostate cancers‡, No.	89	264	125	15		149
Fully adjusted RR*	1.00	0.81 (0.62 to 1.06)	0.68 (0.50 to 0.91)	0.53 (0.30 to 0.94)	.01	0.71 (0.52 to 0.98)
Advanced prostate cancers‡, No	122	374	171	25		204
Fully adjusted RR*	1.00	0.85 (0.68 to 1.07)	0.70 (0.54 to 0.89)	0.67 (0.43 to 1.05)	.02	0.77 (0.59 to 1.01)
Nonadvanced prostate cancers‡, No.	353	1455	688	86		639
Fully adjusted RR*	1.00	0.99 (0.87 to 1.13)	1.04 (0.90 to 1.19)	0.94 (0.74 to 1.20)	.88	0.98 (0.85 to 1.14)

* All relative risks are from a multivariable model adjusted for: age in months, calendar time, race (White, African American, Asian American, Other), height (quartiles), BMI at age 21 (four categories), current BMI (six categories), vigorous physical activity (quintiles), smoking (never, former quit >10 years ago, former quit <10 years ago, current), diabetes (type I or II, yes/no), family history of prostate cancer in father or brother (yes/no), multivitamin use (yes/no), intakes of processed meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, alcohol intake (all quintiles), and energy intake (continuous), and history of prostate-specific antigen testing. Models for decaffeinated coffee are also adjusted for regular coffee intake (continuous). All P values are from two-sided tests. BMI = body mass index.

† Reference group is men who drink no regular or decaffeinated coffee.

‡ Lethal prostate cancer: Prostate cancer death or bone metastases at diagnosis or during follow-up. Advanced: Lethal, or stage T3b, T4, N1 or M1 at diagnosis, or spread to lymph nodes or other metastases during follow-up. Nonadvanced: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

Table 5. Relative risk (RR) and 95% confidence interval (95% CI) of prostate cancer by category of total coffee intake for various latency periods between exposure and diagnosis*

	Total prostate cancer		Advanced cancer†		Nonadvanced cancer†	
	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
0 to 4-year lag, cups per day						
None	810	1.00 (referent)	160	1.00 (referent)	493	1.00 (referent)
<1	1003	.95 (.87 to 1.05)	180	.78 (.62 to .97)	655	1.05 (.93 to 1.18)
1–3	2501	.96 (.89 to 1.05)	436	.77 (.63 to .93)	1592	1.01 (.91 to 1.13)
4–5	587	.97 (.87 to 1.09)	100	.73 (.56 to .95)	389	1.08 (.93 to 1.24)
≥6	134	.81 (.67 to .98)	20	.52 (.33 to .84)	92	.96 (.76 to 1.21)
P _{trend}		.20		.008		.91
4 to 8-year lag, cups per day						
None	745	1.00 (referent)	131	1.00 (referent)	468	1.00 (referent)
<1	886	.92 (.83 to 1.02)	152	.84 (.66 to 1.07)	589	1.00 (.88 to 1.13)
1–3	2267	.93 (.85 to 1.02)	329	.72 (.58 to .89)	1519	1.00 (.89 to 1.11)
4–5	594	.92 (.82 to 1.03)	99	.81 (.61 to 1.07)	397	.97 (.85 to 1.12)
≥6	153	.80 (.67 to .96)	18	.47 (.28 to .78)	102	.88 (.71 to 1.10)
P _{trend}		.06		.008		.34
8 to 12-year lag, cups per day						
None	551	1.00 (referent)	79	1.00 (referent)	360	1.00 (referent)
<1	664	.98 (.87 to 1.10)	91	.85 (.62 to 1.17)	458	1.06 (.92 to 1.22)
1–3	1687	.99 (.89 to 1.10)	181	.68 (.51 to .91)	1175	1.06 (.93 to 1.20)
4–5	465	.91 (.80 to 1.03)	63	.82 (.58 to 1.17)	329	.98 (.83 to 1.14)
≥6	154	.93 (.77 to 1.12)	18	.71 (.42 to 1.21)	111	1.04 (.83 to 1.30)
P _{trend}		.17		.18		.70
12 to 16-year lag, cups per day						
None	389	1.00 (referent)	41	1.00 (referent)	268	1.00 (referent)
<1	448	.97 (.84 to 1.11)	49	.90 (.58 to 1.39)	307	.96 (.81 to 1.14)
1–3	1046	.93 (.82 to 1.06)	93	.72 (.48 to 1.07)	742	.94 (.81 to 1.10)
4–5	353	.97 (.83 to 1.13)	41	.97 (.61 to 1.55)	260	1.02 (.85 to 1.23)
≥6	115	.93 (.75 to 1.16)	8	.59 (.27 to 1.29)	84	.98 (.76 to 1.26)
P _{trend}		.61		.43		.78

* All relative risks are from multivariable models adjusted for: age in months, calendar time, race (White, African American, Asian American, Other), height (quartiles), BMI at age 21 (<20, 20 to <22.5, 22.5 to <25, ≥25 kg/m²), current BMI (<21, 21 to <23, 23 to <25, 25 to <27.5, 27.5 to <30, ≥30 kg/m²), vigorous physical activity (quintiles), smoking (never, former quit >10 years ago, former quit <10 years ago, current), diabetes (type I or II, yes/no), family history of prostate cancer in father or brother (yes/no), multivitamin use (yes/no), intakes of processed meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, alcohol intake (all quintiles), and energy intake (continuous), and history of PSA testing (yes/no, lagged by one period to avoid counting diagnostic PSA tests as screening; collected from 1994 onwards). All P values are from two-sided tests. BMI = body mass index; PSA = prostate-specific antigen.

† Advanced: Lethal, or stage T3b, T4, N1, or M1 at diagnosis, or spread to lymph nodes or other metastases during follow-up. Nonadvanced: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

were adjusted for smoking, thus confounding is a major concern in these studies. Case-control studies are also prone to selection and recall bias.

An association between coffee and lower risk of advanced prostate cancer is biologically plausible. Coffee improves glucose metabolism, has anti-inflammatory and antioxidant effects, and affects sex hormone levels, all of which play roles in prostate cancer progression.

Coffee contains chlorogenic acids (CGAs), which inhibit glucose absorption in the intestine and may favorably alter levels of gut hormones, which affect insulin response (1). Quinides, the roasting products of CGAs, inhibit liver glucose production in experimental models (1). Coffee also contains lignans, phytoestrogens with potent antioxidant activity, which may have positive effects on glucose handling (37). In humans, coffee drinking has been cross-sectionally associated with lower glucose levels after oral glucose loads and better insulin sensitivity (38–40). A cross-sectional study in women found a negative correlation between coffee consumption and circulating C-peptide, a marker of insulin secretion (41).

Insulin may promote tumor progression through the insulin and insulin-like growth factor 1 (IGF-1) receptors in cancer cells. Insulin levels have been associated with a greater risk of cancer progression or mortality among men diagnosed with prostate cancer (9–11), even though insulin has been unassociated (12,13) or inversely associated (14) with overall incidence.

Coffee is a major source of antioxidants and is estimated to provide half of total antioxidant intake in several populations (2,3). Coffee has been associated with improved markers of inflammation in cross-sectional studies and in a recent trial (4,42,43). Inflammation is hypothesized to play a role in the development of prostate cancer through the generation of proliferative inflammatory atrophy lesions (15). Various dietary antioxidants may reduce inflammation and have been associated with lower risk of advanced prostate cancer (44,45).

Coffee drinking may be associated with increased sex hormone-binding globulin (SHBG) and total testosterone levels (5). One study in Greek men found a positive association with estradiol levels but not with SHBG or testosterone (6), whereas another found no association between coffee and sex hormones in young Greek men (7). Coffee has been consistently associated with higher SHBG levels in women (46–49).

Sex hormones play a role in prostate cancer, though the relationships between circulating levels within normal ranges and risk have been difficult to elucidate. It has been hypothesized that although testosterone is necessary for the initial development of prostate cancer, it may limit progression of the disease (50,51). A pooled analysis of 18 prospective studies found an inverse association between SHBG levels and prostate cancer risk (51).

Strengths of our study include the prospective and updated assessment of coffee, long follow-up, and a large number of incident prostate cancers, which allowed us to study stage- and grade-based subtypes. The range of intakes in this cohort was wide, with 16% of men consuming no coffee and 19% of men consuming four or more cups per day. Coffee was accurately reported on FFQs (33), and any misclassification in coffee intake due to differences in cup size or brewing strength would be expected to bias observed associations toward the null and thus would not explain the inverse

associations that we observed. Our use of repeated measures of diet over time captured changes in diet and reduced measurement error (52); however, we were not able to assess coffee intake in young adulthood or total lifetime coffee intake.

This study also has some limitations. First, we relied on self-reported diet, which will inevitably be imperfect. Although coffee is well reported, we assessed usual intake only every 4 years, thus missing shorter-term fluctuations in intakes. In addition, we do not have coffee intake information from earlier periods of life, limiting our ability to determine the most relevant time periods of exposure. Finally, although reverse causation does not appear to explain our findings, we cannot rule it out as a possible source of bias.

In conclusion, men who consumed coffee regularly had a reduced risk of lethal or advanced prostate cancer. It is premature to recommend that men increase coffee intake to reduce advanced prostate cancer risk based on this single study. In addition, the effects of coffee consumption on other aspects of health must be considered in making consumption recommendations. However, our findings are potentially important, given the lack of identified modifiable risk factors for advanced prostate cancer. The association between coffee and prostate cancer should be studied in other prospective cohorts with a wide range of coffee intakes, with control for smoking, and evaluation of lethal or advanced cancers.

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