EUROPEAN UROLOGY ONCOLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Coffee Intake, Caffeine Metabolism Genotype, and Survival Among Men with Prostate Cancer

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Article info

Article history:
Received 18 March 2022
Received in Revised form
26 June 2022
Accepted July 20, 2022

Associate Editor:
Alberto Briganti

Keywords:
Prostatic neoplasms
Coffee
Caffeine
Genetic variation
Mortality

Abstract

Background: Coffee intake may lower prostate cancer risk and progression, but postdiagnosis outcomes by caffeine metabolism genotype are not well characterized.
Objective: To evaluate associations between coffee intake, caffeine metabolism genotype, and survival in a large, multicenter study of men with prostate cancer.
Design, setting, and participants: Data from The PRACTICAL Consortium database for 5727 men with prostate cancer from seven US, Australian, and European studies were included. The cases included had data available for the *CYP1A2* −163C>A rs762551 single-nucleotide variant associated with caffeine metabolism, coffee intake, and >6 mo of follow-up.
Outcome measurements and statistical analysis: Multivariable-adjusted Cox proportional hazards models across pooled patient-level data were used to compare the effect of coffee intake (categorized as low [reference], high, or none/very low) in relation to overall survival (OS) and prostate cancer–specific survival (PCSS), with stratified analyses conducted by clinical disease risk and genotype.
Results and limitations: High coffee intake appeared to be associated with longer PCSS (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.68–1.08; $p = 0.18$) and OS (HR 0.90, 95% CI 0.77–1.07; $p = 0.24$), although results were not statistically significant. In the group with clinically localized disease, high coffee intake was associated with longer PCSS (HR 0.66, 95% CI 0.44–0.98; $p = 0.040$), with comparable results for the group with advanced disease (HR 0.92, 95% CI 0.69–1.23; $p = 0.6$). High coffee intake was associated with longer PCSS among men

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https://doi.org/10.1016/j.euo.2022.07.008

Please cite this article as: J.R. Gregg, J. Kim, C. Logothetis et al., Coffee Intake, Caffeine Metabolism Genotype, and Survival Among Men with Prostate Cancer, Eur Urol Oncol (2022), https://doi.org/10.1016/j.euo.2022.07.008

with the *CYP1A2* AA (HR 0.67, 95% CI 0.49–0.93; $p = 0.017$) but not the AC/CC genotype ($p = 0.8$); an interaction was detected ($p = 0.042$). No associations with OS were observed in subgroup analyses ($p > 0.05$). Limitations include the nominal statistical significance and residual confounding.

Conclusions: Coffee intake was associated with longer PCSS among men with a *CYP1A2* −163AA (*1F/*1F) genotype, a finding that will require further replication.

Patient summary: It is likely that coffee intake is associated with longer prostate cancer–specific survival in certain groups, but more research is needed to fully understand which men may benefit and why.

1. Introduction

Coffee contains numerous plant-derived antioxidant and bioactive compounds known to lower systemic inflammation [1]. Coffee therefore offers the potential to impact the progression of solid malignancies, and its intake has been associated with lower rates of colorectal cancer recurrence and related mortality [2]. Higher coffee intake has been linked to lower prostate cancer risk [3], although few studies have evaluated associations between coffee intake and survival following prostate cancer diagnosis.

The −163A>C (rs762551) single-nucleotide variant (SNV; *1F allele) is indicative of cytochrome P450 1A2 (CYP1A2) enzyme activity [4] and has been used to categorize individuals as fast or slow caffeine metabolizers [5,6]. In a clinical cohort of patients diagnosed with localized prostate cancer and managed on active surveillance, we previously observed that high coffee intake among men with a fast caffeine metabolism genotype was safe and possibly protective in terms of disease progression [7]. However, the association of coffee intake with caffeine metabolism genotype has not been fully investigated in a broader cohort of men at risk of prostate cancer–specific death.

We therefore sought to determine associations between coffee intake, rs762551 genotype, and survival using a large consortium database of prostate cancer cases followed for death due to prostate cancer and other causes. We hypothesized that higher coffee intake would be associated with prostate cancer specific–survival, particularly for men who are fast caffeine metabolizers.

2. Patients and methods

2.1. Studies and cases

We included data for prostate cancer cases across studies in The PRACTICAL Consortium (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; http://www.icr.ac.uk/our-research/research-divisions/division-of-genetics-and-epidemiology/oncogenetics/research-projects/ukgpcs/ukgpcs-collaborators). Details regarding individual studies have been published separately [8]. Data were included for men of European ancestry who met the following criteria: (1) had genotype data for the SNV of interest (*CYP1A2* −163C>A rs762551) available; (2) data available on usual coffee intake at study enrollment/before diagnosis; (3) at least 6 mo of follow-up (ie, survival of ≥6 mo following study entry); and (4) enrolled in studies in which at more than ten events (death from any cause or prostate cancer) occurred. All of the studies met the ethics criteria in their respective countries in accordance with the Declaration of Helsinki.

2.2. Genotyping

The caffeine metabolism–related *CYP1A2* −163C>A genotype was determined using two different genotyping chips. Where available, the SNV was typed directly using an Illumina Custom Infinium genotyping array. This array was designed for the Collaborative Oncological Gene-Environment Study and consisted of 211 155 SNVs, as previously described [9]. SNV data were also obtained via imputation using the OncoArray chip as previously described [10]. Full details of the genotyping and imputation have been published previously [8,10,11].

2.3. Cancer risk stratification

Cases were stratified by disease aggression on the basis of pathologic and staging-related data. Cases were categorized as "localized and low risk" disease if Surveillance, Epidemiology, and End Results (SEER) staging indicated localized disease at diagnosis or if SEER staging was not available and Gleason grade group was documented as 1 and TNM staging indicated the absence of nodal or metastatic disease. Cases were categorized as "regional" disease if SEER staging or TNM staging indicated regional or nodal disease in the absence of metastatic disease. Cases with SEER staging or TNM staging indicating metastatic disease were classified as "metastatic" disease. All other cases were classified as "unknown".

2.4. All-cause and prostate cancer–specific mortality

Follow-up was carried out in each individual study as previously specified [9]. Cases with >6 mo of follow-up were included and were censored at the date of last follow-up or death. Cases with unknown cause or other cause of death were classified as non–prostate cancer–specific mortality.

2.5. Coffee consumption

Coffee consumption before prostate cancer diagnosis was assessed using various comparable formats querying the frequency of usual intake and assuming a standard portion or cup size. While all men in this study were enrolled fol-

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lowing a diagnosis of prostate cancer, queries for usual coffee consumption referred to an intake period of ≥6 mo (PRAGGA), 1 yr (ESTHER, MCCS, and PLCO), 2 yr (FHCRC), or 5 yr (UKGPCS, MCC-Spain) before prostate cancer diagnosis (see Supplementary Table 1 for additional information). Coffee intake categories were defined following consideration of the data distribution across cohorts, evaluation of cubic splines in the pooled model, coffee intake frequencies assessed in food frequency questionnaires (Supplementary Table 1), and the literature on chronic disease (further details and spline plots are provided in Supplementary Fig. 1) [12]. For ease of interpretation and because of known changes in intake and energy balance that occur in some patients following a diagnosis of metastatic cancer, we aimed to compare habitual coffee consumers with "low" and "high" intake. Low consumption was defined as three or more cups/wk up to two cups/d (reference) and high consumption as more than two cups/d. None/very low consumption (from zero to three or more cups/wk) was retained as a separate category.

2.6. Statistical analysis

All analyses were conducted using STATA v16.1 (StataCorp, College Station, TX, USA). Descriptive statistics were used to describe baseline characteristics, including coffee consumption and tumor-related factors, by study and survival status. Cox proportional-hazards models using pooled individual-level data [13] stratified by study site were used to evaluate the association of coffee intake with PCSS. The primary multivariable models were adjusted for age at diagnosis, cancer stage/aggression, body mass index, and smoking status. We further assessed additional clinical factors that were not complete for all cohorts: prior prostate surgery or radiation, androgen deprivation therapy use, prostate-specific antigen level, and physical activity (Supplementary Table 4 shows the variable stratification). Based on our prior report for active surveillance patients [7], we conducted preplanned analysis by clinical risk group. "Low risk" was defined as those with known localized or grade group 1 disease without nodal or distant metastases. "High risk" was defined as node-positive, metastatic, or unknown disease. We then stratified patients by *CYP1A2* rs762551 genotype, combining the AC and CC genotypes because of the low frequency of the C allele. Multivariable Cox proportional-hazards models were generated for each genotype, and an interaction model between coffee intake and genotype was fitted (with p values reported for interaction terms). Proportional-hazards assumption testing was performed for all models using Schoenfeld residuals. All statistical tests were two-sided and results were considered statistically significant if $p < 0.05$.

2.7. Data availability

The data analyzed in this study are available from The PRACTICAL Consortium. Some restrictions apply to availability, but the data are available from the authors on request with the permission of The PRACTICAL Consortium.

3. Results

A total of 5727 cases from seven studies met the inclusion criteria. Median follow-up for those who did not die of prostate cancer was 5.1 yr (interquartile range [IQR] 2.1–7.8). In the overall cohort there were 906 deaths, of which 481 (53%) were due to prostate cancer. Case characteristics varied by study site and are displayed in Table 1. Across all studies, the median age was 63 yr (IQR 58–70) and the median coffee consumption among consumers was 2.5 cups/d (IQR 1–2.5).

Table 2 shows coffee intake in relation to PCSS for all men and by clinical risk group. High intake (compared to low/intermediate) was associated with a modest improvement in PCSS in the overall cohort (HR 0.85, 95% CI 0.68–1.08; $p = 0.18$), with similar results observed following additional adjustment for clinical factors (HR 0.86, 95% CI 0.68–1.08; $p = 0.19$; data in text only), although the results were not statistically significant. In the group with clinical low-risk (localized) disease, high intake was nominally associated with longer PCSS (HR 0.66, 95% CI 0.44–0.98; $p = 0.040$), with comparable (interaction $p = 0.3$) albeit attenuated results in the high-risk group (HR 0.92, 95% CI 0.69–1.27; $p = 0.6$). Coffee intake was not significantly associated with OS in the overall cohort or in the high or low risk groups, with the exception that none/very low coffee intake was possibly associated with a higher risk of progression in the overall cohort when compared to low/intermediate intake (HR 1.20, 95% CI 1.00–1.44; $p = 0.047$; Supplementary Table 2).

Table 3 shows coffee intake in relation to PCSS stratified by rs762551 caffeine metabolism genotype. High coffee intake was nominally associated with longer PCSS among those with the AA genotype (HR 0.67, 95% CI 0.49–0.93; $p = 0.017$) but not the AC/CC genotype (HR 1.04, 95% CI 0.74–1.47, $p = 0.8$) and a significant interaction was detected ($p = 0.042$). High coffee intake was not associated with longer OS among those with the AA or AC/CC genotype, and no significant interactions were detected (all $p > 0.05$; Supplementary Table 3).

4. Discussion

We evaluated the association of coffee intake and caffeine metabolism genotype (CYP1A2 −163C>A rs762551, *1F allele) with survival in a large international cohort of Caucasian men with prostate cancer followed for PCSS and OS. While coffee intake was not significantly associated with PCSS or OS in the overall cohort, a nominally significant association was observed between high coffee intake (compared to low/intermediate) and longer PCSS in the groups with (1) less aggressive prostate cancer and (2) the CYP1A2 −163AA (*1F/*1F) fast caffeine metabolizer genotype (interaction $p = 0.042$).

To the best of our knowledge, this is the first study to evaluate associations of coffee intake and caffeine metabolism genotype with survival in a wide-range of men with prostate cancer. Prior investigations have shown that the

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Table 1 – Characteristics of prostate cancer cases by study site

	ESTHER	FHCRC	MCC-Spain	MCCS	PLCO	PRAGGA	UKGPCS	Total
Patients (*n*)	502	592	488	872	488	111	2,674	5,727
Median age yr (IQR)[a]	65.7 (62.2–68.4)	63.0 (57.0–68.0)	66.6 (61.7–72.1)	68.4 (63.6–73.7)	72.0 (68.0–76.0)	58.9 (55.7–62.9)	58.9 (55.7–62.9)	63.0 (57.9–69.5)
Median PSA, ng/ml (IQR)	6.9 (4.1–13.9)	6.1 (4.6–9.5)	5.8 (7.5–10.3)	7.7 (5.6–12.7)	5.8 (4.6–8.1)	9.5 (6.4–15.3)	7.8 (4.6–16.0)	6.7 (4.5–12)
PSA quartile, *n* (%)								
1st (0–4.46 ng/ml)	106 (21)	118 (20)	32 (7)	241 (28)	91 (19)	6 (5)	592 (22)	1,186 (21)
2nd (4.50–6.73 ng/ml)	78 (16)	214 (36)	160 (33)	55 (6)	174 (36)	22 (20)	517 (19)	1,220 (21)
3rd (6.74–11.97 ng/ml)	74 (15)	131 (22)	200 (41)	54 (6)	117 (24)	34 (31)	574 (22)	1,184 (21)
4th (≥12 ng/ml)	111 (22)	95 (16)	94 (19)	47 (5)	47 (10)	34 (31)	794 (30)	1,222 (21)
Unknown	133 (27)	34 (6)	2 (0.4)	475 (55)	59 (12)	15 (14)	197 (7)	915 (16)
Disease category, *n* (%)[a,b]								
Localized or low risk	332 (66)	484 (82)	435 (90)	789 (91)	231 (47)	78 (70)	1,459 (55)	3,808 (67)
Regional	135 (27)	96 (16)	28 (5.7)	47 (5.4)	0 (0)	28 (25)	596 (22)	930 (16)
Advanced	18 (3.6)	12 (2.0)	7 (1.4)	5 (0.6)	0 (0)	0 (0)	155 (5.8)	197 (3.4)
Unknown	17 (3.4)	0 (0)	18 (3.7)	31 (3.6)	257 (53)	5 (4.5)	464 (17)	792 (14)
Gleason grade group, *n* (%)								
1	262 (52)	313 (53)	194 (40)	385 (44)	231 (47)	46 (41)	2,375 (42)	2,375 (42)
2 or 3	182 (36)	217 (37)	212 (43)	283 (33)	188 (39)	42 (38)	2,067 (36)	2,067 (36)
4 or 5	44 (8.8)	60 (10)	78 (16)	129 (15)	65 (13)	17 (15)	835 (15)	835 (15)
Unknown	14 (2.8)	2 (0.3)	4 (0.8)	75 (8.6)	4 (0.8)	6 (5.4)	450 (7.9)	450 (7.9)
SEER stage, *n* (%)								
Localized	292 (58)	484 (82)	409 (84)	786 (91)	0 (0)	78 (70)	1,346 (51)	3,395 (60)
Regional	135 (27)	96 (16)	28 (5.7)	47 (5.4)	0 (0)	28 (25)	596 (23)	930 (16)
Metastatic	14 (2.8)	12 (2.0)	7 (1.4)	5 (0.6)	0 (0)	0 (0)	155 (5.9)	193 (3.4)
Unknown	61 (12.2)	0 (0)	44 (9.0)	29 (3.3)	488 (100)	5 (4.5)	1,165 (21)	1,165 (21)
N stage, *n* (%)								
N0	365 (73)	0 (0)	431 (88)	57 (8.6)	0 (0)	82 (74)	1,339 (54)	2,274 (43)
N1	33 (6.6)	0 (0)	5 (1.0)	2 (0.3)	0 (0)	1 (0.9)	162 (6.5)	203 (3.8)
Unknown	102 (20)	592 (100)	52 (11)	604 (91)	488 (100)	28 (25)	984 (40)	2,850 (54)
M stage, *n* (%)								
M0	351 (73.3)	0 (0)	428 (87.7)	0 (0)	0 (0)	84 (75.7)	1,185 (48.1)	2,048 (38.9)
M1	16 (3.3)	0 (0)	7 (1.4)	5 (0.8)	0 (0)	0 (0)	155 (6.3)	183 (3.5)
Unknown	112 (23)	592 (100)	53 (11)	633 (99)	488 (100)	27 (24)	1,125 (46)	3,030 (58)
Localized treatment, *n* (%)								
Surgery and/or radiation	31 (6.2)	0 (0)	44 (9.0)	44 (5.1)	7 (1.4)	32 (29)	191 (7.1)	349 (6.1)
None	471 (94)	0 (0)	429 (88)	340 (39)	375 (77)	79 (71.2)	2,483 (93)	4,177 (73)
Unknown	0 (0)	592 (100)	15 (3.1)	488 (56)	106 (22)	0 (0)	0 (0)	1,201 (21)
ADT use, *n* (%)								
No	388 (77)	0 (0)	308 (63)	0 (0)	255 (52)	38 (34)	1,449 (54)	2,438 (43)
Yes	114 (23)	0 (0)	151 (31)	0 (0)	127 (26)	73 (66)	1,225 (46)	1,690 (30)
Unknown	0 (0)	592 (100)	29 (5.9)	872 (100)	106 (22)	0(0)	1,599 (28)	1,599 (28)
Smoking status, *n* (%)[a]								
Never smoker	172 (34)	255 (43)	147 (30)	404 (46)	205 (42)	42 (38)	1120 (42)	2345 (41)
Former smoker	266 (52)	289 (49)	226 (46)	393 (45)	227 (47)	42 (38)	1281 (48)	2724 (48)
Active smoker	58 (12)	48 (8.1)	113 (23)	75 (8.6)	56 (12)	12 (11)	264 (9.9)	626 (11)
Unknown	6 (1.2)	0 (0)	2 (0.4)	0 (0)	0 (0)	15 (14)	9 (0.3)	32 (0.6)
Overall physical activity, *n* (%)								
Low or sedentary	177 (35)	222 (38)	304 (62)	0 (0)	0 (0)	63 (57)	74 (2.8)	840 (15)
Moderate	136 (27)	343 (58)	83 (17)	2 (0.2)	0 (0)	16 (14)	517 (20)	1097 (19)
High or energetic	117 (23)	27 (4.6)	101 (21)	1 (0.1)	0 (0)	7 (6.3)	2065 (77)	2318 (41)
Unknown	72 (14.3)	0 (0)	0 (0)	869 (100)	488 (100)	25 (23)	16 (0.6)	1472 (26)
Body mass index, *n* (%)								
>18.5 and <25 kg/m^2	164 (33)	188 (32)	108 (22)	203 (23)	120 (25)	20 (18)	565 (21)	1368 (24)
≥25 and <30 kg/m^2	240 (48)	282 (48)	264 (54)	435 (50)	267 (55)	46 (41)	1320 (49)	2854 (50)
≥30 and <35 kg/m^2	69 (14)	96 (16)	96 (17)	128 (15)	78 (16)	21 (19)	547 (20)	1035 (18)
≥35 kg/m^2	17 (3.4)	26 (4.4)	16 (3.3)	10 (1.2)	16 (3.3)	7 (6.3)	181 (6.8)	273 (4.8)
Unknown	12 (2.4)	0 (0)	4 (0.8)	96 (11.0)	7 (1.4)	17 (15.3)	61 (2.3)	197 (3.4)
Coffee intake, *n* (%)								
None/very low (0 to ≤3 cups/wk)	114 (23)	184 (31)	70 (14)	230 (26)	123 (25)	35 (32)	767 (29)	1523 (27)
Low (>3 cups/wk to 2 cups/d)	187 (37)	132 (22)	102 (21)	194 (22)	78 (16)	49 (44)	656 (24)	1398 (24)
High (>2 cups/d)	201 (40)	276 (47)	316 (65)	448 (51)	287 (59)	27 (24)	1251 (47)	2806 (49)
Median follow-up, yr (IQR)	5.5 (4.8–6.3)	12.5 (11.3–13.5)	6.0 (5.0–6.9)	7.8 (5.5–13.2)	2.0 (1.0–2.0)	8.9 (7.2–10.8)	3.3 (1.5–5.5)	5.1 (2.2–4.4)
Person-years at PCSM risk	1390	6901	2783	8206	1099	1024	6623	28 026

ADT = androgen deprivation therapy; IQR = interquartile range; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen; SEER = Surveillance, Epidemiology, and End Results.

[a] Indicates a variable included in multivariable Cox proportional-hazards models.

[b] "Disease category" is a composite variable defined as follows: Localized or low risk = SEER stage 1 disease or SEER staging unknown and Gleason grade group 1; Regional = SEER stage 2 or N stage 2; Metastatic = SEER stage 3 or M stage 1; Unknown = none of the preceding criteria are met.

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Table 2 – Coffee intake in relation to prostate cancer–specific survival among all men and by clinical risk group: pooled analysis of The PRACTICAL Consortium (n = 5727)

Coffee intake[a]	*n*	Events	HR (95% CI)[b]	*p* value*
Prostate cancer-specific survival				
None/very low	1513	146	1.15 (0.90–1.48)	0.3
Low	1387	121	1.00 (reference)	
High	2767	214	0.85 (0.68–1.08)	0.18
Low risk: localized or confirmed nonmetastatic GG 1 disease				
None/very low	1014	48	0.87 (0.57–1.33)	0.5
Low	892	42	1.00 (reference)	
High	1846	62	0.66 (0.44–0.98)	0.040
High risk: node-positive, distant metastatic, or unknown disease				
None/very low	308	76	1.27 (0.93–1.72)	0.13
Low	296	54	1.00 (reference)	
High	521	110	0.92 (0.69–1.23)	0.6

CI = confidence interval; GG 1 = Gleason grade group 1; HR = hazard ratio.
* $p = 0.3$ for interaction between respect to high intake and clinical group; $p = 0.3$ for interaction between none/very low intake and clinical group.
[a] None/very low = 0 to <3 cups weekly; Low ≥3 cups weekly to up to 3 cups daily; High ≥2 cups daily.
[b] Multivariable adjustment for age, stage, body mass index, and smoking status; stratified by study site.

Table 3 – Coffee intake in relation to prostate cancer–specific survival by rs762551 caffeine metabolism genotype: pooled analysis of The PRACTICAL Consortium (n = 5727)

Coffee	AA genotype[b]			AC/CC genotype[b]			Interaction
intake[a]	*n* (events)	HR (95% CI)	*p* value	*n* (events)	HR (95% CI)	*p* value	*p* value
None/very low	762 (72)	1.02 (0.72–1.46)	0.9	751 (74)	1.27 (0.88–1.82)	0.20	0.4
Low	674 (63)	1.00 (reference)		713 (58)	1.00 (reference)		
High	**1430 (104)**	**0.67 (0.49–0.93)**	**0.017**	1,337 (110)	1.04 (0.74–1.47)	0.8	**0.042**

CI = confidence interval; HR = hazard ratio, with multivariable adjustment for age, staging, body mass index, and smoking status, stratified by study site.
[a] None/very low = 0 to <3 cups weekly; Low ≥3 cups weekly to up to 3 cups daily; High ≥2 cups daily.
[b] For *CYP1A2* rs762551, 2895 (50.6%) had the AA, 2381 (41.6%), had the AC, and 451 (7.8%) had the CC genotype, giving a frequency of 71.3% for the A allele, which is consistent with allele frequencies in populations of European ancestry (dbSNP; www.ncbi.nlm.nih.gov/snp/rs762551). Results were consistent with Hardy-Weinberg equilibrium ($p > 0.05$).

risk of a prostate cancer diagnosis [3] and the development of aggressive disease [14] may be lower among coffee consumers. However, few studies have evaluated risk of disease progression or mortality following a prostate cancer diagnosis. While our finding that high coffee intake appears to be associated with a modest improvement in PCSS is not statistically significant (HR 0.85, 95% CI 0.68–1.08; $p = 0.18$), it is consistent with data on associations between coffee intake and colorectal cancer diagnosis and aggression. In a large investigation of patients with colorectal cancer, coffee intake was inversely associated with cancer recurrence and mortality in the presence of stage III disease [2], and levels of metabolites associated with coffee consumption were associated with a lower risk of colorectal cancer incidence or diagnosis [15].

In addition, our group previously showed that in an unselected group of men with generally indolent prostate cancer managed on active surveillance, coffee intake was associated with longer progression-free survival, although the results were not significant. Our current findings provide evidence that coffee consumption may be especially relevant for men with presumed localized prostate cancer (some of whom may be managed on active surveillance), demonstrating a nominally significant association of high coffee intake (two or morecups/d) with longer PCSS in this group. Men on active surveillance are a highly motivated population, and future investigations demonstrating associations between modified coffee intake and slowed (or halted) disease progression among selected men would offer the potential to avoid or delay radical treatment for prostate cancer, which can affect men's quality of life [16].

Our finding of a significant interaction between *CYP1A2* −163AA (*1F/*1F) caffeine metabolism genotype and coffee consumption is relevant both for the planning of future clinical studies and informing future investigations of a potential mechanism. Our prior work in active surveillance cohorts suggests that coffee intake may be associated with longer progression-free survival for men with the fast caffeine metabolism genotype [7]. Studies in other disciplines have demonstrated similar interaction effects for the association of coffee intake with genotype for this SNV on health-related outcomes. Prior findings include a lower risk of myocardial infarction in long-term prospective studies [17] and better athletic performance among fast metabolizers who consume caffeine in randomized trials [5,6]. In our work, coffee consumption among fast caffeine metabolizers was associated with longer PCSS, suggesting that future studies investigating coffee consumption as a means to augment prostate cancer treatment plans may demonstrate a benefit in specific populations, such as those with the fast caffeine metabolism genotype.

This study also offers mechanistic insights into the association between coffee intake and PCSS. It is established that coffee contains numerous antioxidant and bioactive compounds that may lower systemic inflammation [1]; it has been shown that extracts following coffee roasting can decrease tumor growth in cell-line and mouse prostate cancer models [18]. In comparison, evidence describing the

Please cite this article as: J.R. Gregg, J. Kim, C. Logothetis et al., Coffee Intake, Caffeine Metabolism Genotype, and Survival Among Men with Prostate Cancer, Eur Urol Oncol (2022), https://doi.org/10.1016/j.euo.2022.07.008

effects of caffeine are mixed, as caffeine can affect cells via a myriad of mechanisms, including changes in DNA repair and apoptosis [19], as well as higher levels of circulating testosterone and androgen receptor expression [20], key signaling hormones in prostate cancer progression. These data, in conjunction with our findings, raise the possibility that protective compounds present in coffee may be counteracted by the potentially deleterious effects of caffeine (which may also be mitigated by more rapid caffeine metabolism). Therefore, further studies are needed to evaluate coffee and caffeine metabolites and their association with oncologically relevant outcomes. This work is ongoing with the goal of identifying a patient population (eg, that defined by caffeine metabolism genotype) and intermediate biomarkers (eg, coffee metabolites) for whom caffeinated coffee "prescriptions" may be targeted and monitored.

Our study is limited by residual or unmeasured confounding, including that due to population stratification and incomplete data on prognostic factors, diet and lifestyle habits, as well as sample size. Furthermore, self-reported coffee intake recalled when completing standardized questionnaires is inherently limited in its accuracy and detail, and amounts (eg, more than two cups/d) should not be overinterpreted given that serving sizes, coffee preparation methods, and the temporality or time frame of assessment may vary. In addition, few studies have separately assessed decaffeinated coffee consumption, which is expected to be relatively low among habitual coffee consumers and/or fast caffeine metabolizers [21] (for whom our most notable findings were observed). Finally, the current study includes only men of European ancestry, limiting its broader applicability. This is especially relevant given that African Americans are at higher risk of prostate cancer diagnosis and death, representing the most pronounced racial disparity among tumors [22]. Importantly, the frequency of the rs762551 C allele is higher in African American and African populations (https://www.ncbi.nlm.nih.gov/snp/rs762551), a phenomenon that was confirmed in a broader sample of men with prostate cancer in The PRACTICAL Consortium database (data not shown), suggesting that further studies should evaluate coffee intake and caffeine metabolism genotype among African American men.

In summary, our analysis of a large cohort of prostate cancer cases demonstrates that increased coffee intake is nominally associated with PCSS following a diagnosis of prostate cancer among men with clinically localized disease and fast caffeine metabolism genotype. Future studies evaluating coffee and caffeine intake in men following prostate cancer diagnosis are needed to replicate our findings, especially when considering the development of diet-based or other clinical interventions to augment prostate cancer treatment and lengthen patient life.

5. Conclusions

Coffee intake was associated with longer PCSS and OS in a large cohort of men diagnosed with prostate cancer, although the results are not statistically significant. Among men with the *CYP1A2* −163AA (*1F/*1F) caffeine metabolism genotype, coffee intake was nominally associated with longer PCSS. Future work is needed to replicate these findings, to determine the specific populations (such as those with a fast caffeine metabolism genotype) in which coffee-based interventions or coffee intake "prescriptions" could be beneficial, and to define the mechanisms through which coffee- and caffeine-related metabolites impact prostate cancer progression.

Author contributions: Justin R. Gregg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gregg, Kim, Daniel, Wei.
Acquisition of data: Logothetis, Muir, UKGPCS Collaborative Group, Giles, Stanford, Berndt, Kogevinas, Brenner, Eeles, The PRACTICAL Consortium.
Analysis and interpretation of data: Gregg, Daniel, Zhang, Hanash, Manyam.
Drafting of the manuscript: Gregg.
Critical revision of the manuscript for important intellectual content: Wei, Daniel, Gregg.
Statistical analysis: Gregg, Wei, Daniel.
Obtaining funding: Gregg.
Administrative, technical, or material support: The PRACTICAL Consortium.
Supervision: Daniel, Wei, Hanash.
Other: None.

Financial disclosures: Justin R. Gregg certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Justin R. Gregg serves on an advisory board for Bayer. The remaining authors have nothing to disclose.

***Funding/Support and role of the sponsor*:** This study was supported by a National Institutes of Health/National Cancer Institute cancer center support grant (P30 CA016672), a Department of Defense PCRP early career investigator award (W81XWH-18-1-0173 to J.R.G.), and an American Institute for Cancer research investigator-initiated research grant (FP00011072 to J.R.G.). The sponsors played no direct role in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.07.008.

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