Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition

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For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php

Key words Coffee, tea, decaffeinated, caffeinated, prostate cancer, EPIC

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
EPIC	European Prospective Investigation into Cancer and Nutrition
HR	Hazard Ratio
RR	Relative Risk
TNM	Tumor Node-metastasis
WCRF	World Cancer Research Fund

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Novelty and impact

Numerous studies have assessed the association of coffee and tea consumption with risk of total prostate cancer and results are inconsistent. Total prostate cancer mainly reflects propensity to have a biopsy; hence, more attention must be given to advanced and fatal disease. Few cohort studies have so far examined these associations according to disease stage, grade or fatality. Our findings from this large prospective cohort study does not support any association between drinking tea or coffee, with or without caffeine, and risk of total prostate cancer or cancer by stage, grade or fatality.

ABSTRACT

The epidemiological evidence regarding the association of coffee and tea consumption with prostate cancer risk is inconclusive, and few cohort studies have assessed these associations by disease stage and grade. We examined the associations of coffee (total, caffeinated and decaffeinated) and tea intake with prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition. Among 142,196 men, 7,036 incident prostate cancer cases were diagnosed over 14 years of follow-up. Data on coffee and tea consumption were collected through validated country-specific food questionnaires at baseline. We used Cox proportional hazards regression models to compute hazard ratios (HRs) and 95% confidence intervals (CI). Models were stratified by center and age, and adjusted for anthropometric, lifestyle and dietary factors. Median coffee and tea intake were 375 mL/day and 106 mL/day, respectively, but large variations existed by country. Comparing the highest (median of 855 mL/day) versus lowest (median of 103 mL/day) consumers of coffee and tea (450 mL/day versus 12 mL/day) the HRs were 1.02 (95% CI, 0.94-1.09) and 0.98 (95% CI, 0.90-1.07) for risk of total prostate cancer, and 0.97 (95% CI, 0.79-1.21) and 0.89 (95% CI, 0.70-1.13) for risk of fatal disease, respectively. No evidence of association was seen for consumption of total, caffeinated or decaffeinated coffee or tea and risk of total prostate cancer or cancer by stage, grade or fatality in this large cohort. Further investigations are needed to confirm these findings and clarify whether an association exists by different preparations or by concentrations and constituents of these beverages.

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer amongst men in developed nations, and the age-standardized incidence rate of prostate cancer has been generally increasing worldwide [1-3]. This increase in incidence was presumably due to the introduction of prostate specific-antigen screening [3]. The etiology of this malignancy remains largely unclear, as only old age, black race, positive family history, prostate cancer susceptibility polymorphisms and possibly height and high circulating insulin-like growth factor I concentrations are established risk factors [4-7]. No dietary risk factors for prostate cancer have been firmly established [7, 8].

Tea and coffee are the two most widely consumed beverages in the world. In-vitro and animal studies have suggested that anti-oxidative and anti-inflammatory properties of polyphenols present in coffee and tea, such as catechins and diterpenes, might reduce the risk of prostate cancer [9-11].

The association between coffee, tea and risk of total prostate cancer risk has been widely investigated in epidemiological studies, but the findings are inconsistent[8, 12-15]. Most cohort studies have reported null associations, but many studies were limited by relatively small sample sizes, short follow-up time, lack of detailed adjustment for potential confounders, lack of information on coffee types and preparations, and scarce cancer stage and grade information. Hence, in the present large prospective study, we aimed to examine the association of coffee (total, caffeinated, decaffeinated) and tea intake with risk of total prostate cancer or risk by stage, grade and fatality in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

MATERIAL AND METHODS

Study Design

EPIC is an ongoing multicenter prospective cohort study designed to investigate risk factors of cancer and other chronic diseases. There are 23 EPIC centers in 10 European countries (i.e. Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and United Kingdom [UK]) that recruited more than half a million participants in the 1990s. Details about the cohort population and the data collection procedures have been described elsewhere [16].

In the present study, participants from France and Norway, Naples (Italy) and Utrecht (The Netherlands) were excluded because these centers included only women. Data from 142,196 male participants were included for analysis after excluding 3,972 men with prevalent cancers (other than non-melanoma skin cancer) at recruitment, and 5,766 men with incomplete dietary or non-dietary information or men with an extreme energy intake relative to estimated energy requirement. All subjects gave written informed consent and the Institutional Review Boards of the International Agency for Research on Cancer and of all EPIC recruitment centers approved the study.

Exposure Assessment

Dietary assessment over the 12 months before recruitment was recorded using validated country-specific food questionnaires including a range of 88 to 266 food items. Questionnaires were usually self-administered, except in Greece, Spain and Ragusa in Italy, where trained interviewers were used. Data on caffeinated and decaffeinated coffee were not available in the EPIC centers of Ragusa (Italy), Umeå (Sweden) and Denmark, whereas data on decaffeinated coffee was not available in

Malmö (Sweden). Further details on the diet questionnaires and their validation are described elsewhere [16, 17]. The recorded number of cups of coffee and tea consumed per day, week, or month were converted to millilitres per day (ml/day). This conversion was completed by each center as the cup sizes varied between countries. As coffee and tea intake differed substantially by country, country-specific fourths or thirds for these beverages were used based on the distribution of intake among controls after excluding the non-consumers at recruitment.

Assessment of Prostate Cancer

A total of 7,036 men were diagnosed with first incident prostate cancer according to the International Classification of Diseases 10th revision code. Follow-up began from the date of recruitment and ended at either the date of diagnosis of prostate cancer, date of death due to any reason or last known contact, or end of follow-up through 2015, whichever came first. Incident prostate cancer diagnoses were based on population-based cancer registries in Denmark, Italy, The Netherlands, Spain, Sweden, and the UK. An active follow-up including direct or next of kin communication and/or combination of different sources of ascertainment including health insurance records, regional health departments, municipality registries, hospital records and pathology registries were used in Germany and Greece. Of the 7,036 incident prostate cancer cases, 4,030 (57%) had stage information and 4,483 cases (64%) had grade information. Tumours were classified as localized (tumor-node-metastasis [TNM] staging score of T0-T2 and N0/Nx and M0, or stage coded in the recruitment center as localized; n= 2,641) or advanced prostate cancer (T3-T4 and/or N1-N3 and/or M1, or stage coded in the recruitment center as metastatic; n= 1,389). Further, tumours were classified as low-intermediate grade (Gleason score of <8, or

grade coded as well, moderately, or poorly differentiated; n=3,757) or high-grade prostate cancer (Gleason score of ≥8, or grade coded as undifferentiated; n=726). During the follow-up period, 936 fatal cases of prostate cancer were identified.

Statistical Analysis

Hazard ratios (HR) and 95% confidence intervals (CIs) were computed for the associations between coffee and tea intake and risk for prostate cancer using Cox proportional hazards regression models with age as the underlying time-scale. The models were stratified for age at recruitment in 5-year intervals (<50, 50-54, 55-59, 60-64, 65-69, ≥70 years) and EPIC-participating center to control for differences in recruitment or follow-up procedures and questionnaires format. The proportionality of hazards was verified based on the slope of the Schoenfeld residuals over time, and no evidence of violation was detected.

The multivariable models were adjusted for a set of a *priori*-determined covariates that included smoking status (never, former, current or missing), education (up to high school, university graduate, or missing), body mass index (BMI in fifths: <23.6, ≥23.6 to < 25.5, ≥25.5 to < 27.2, ≥27.2 to < 29.4, ≥ 29.4 kg/m^2, or missing), physical activity index [18] (inactive, moderate inactive, moderate active, active, or missing), history of diabetes (no, yes, missing), alcohol (non-consumers, <5, 5-14.9, 15-29.9, or >30 g/day), and intake of total energy (continuous in kcal/day), fish (continuous, g/day), calcium (continuous, mg/day), and fruits and vegetables (continuous, g/day). Coffee and tea intake were further mutually adjusted for each other in respective models. Similarly, caffeinated coffee and decaffeinated coffee were mutually adjusted. Missing values were assigned to separate categories for

smoking status (1.4%), education (2.7%), physical activity (2.2%), and diabetes (9.4%).

The consumption of coffee and tea was modeled with both categorical (country-specific fourths or thirds) and continuous terms (per 200 mL for coffee or 100 mL for caffeinated coffee and tea or 50 mL for decaffeinated coffee, depending on the range of intake of each beverage type). Non-consumers were defined as participants who did not consume the beverage under evaluation at recruitment, but could consume other beverages. For categorical analyses, the low consumers were used as the reference category. In separate analyses, we included a quadratic term for coffee or tea consumption to assess potential nonlinear associations.

We also assessed potential interactions on the multiplicative scale by age at enrollment (<60 vs. ≥ 60 years), smoking status (never vs. ever smokers), BMI (<25, 25-29.9, ≥30 Kg/m^2) and physical activity (inactive and moderately inactive vs. moderately active and active). Multiplicative interaction terms were incorporated to the models and likelihood-ratio tests were used to test for interaction. Country-specific analyses were also performed. Heterogeneity of associations across countries and by stage and grade of prostate cancer was explored using the Cochran's Q test and the I^2 metric of inconsistency.

A range of sensitivity analyses were also performed by (i) excluding men diagnosed with prostate cancer in the first two years of follow-up to limit the likelihood that the observed associations were due to change of coffee or tea consumption produced by extant cancers, (ii) performing further adjustments for employment, height, waist circumference, hip circumference, waist-to-hip ratio, red and processed meat consumption and a more detailed variable for smoking status (never, former quit ≤10 years ago, former quit 11-20 years ago, former quit >20 years

ago, current with 1-15 cigarettes/day, current with 16-25 cigarettes/day, current with >25 cigarettes/day, current with pipe/cigar or occasional use), or (iii) considering non-consumers as the reference group. When Gleason score cut-point of 7 (instead of 8) was used to define prostate cancer grade or when T3a tumours were not considered as advanced cases in additional sensitivity analyses, the associations of coffee and tea intake in relation to prostate cancer were very similar (data not shown).

All P-values were two-sided and statistical analyses were conducted using STATA version 14 (Stata Corp, college Station, TX).

RESULTS

Supplemental Table 1 describes the baseline distribution of exposure and outcome information by country in EPIC. A total of 7,036 men were diagnosed with prostate cancer after a mean 14 years of follow-up. The mean age at enrolment in the cohort was 52 years. Of the 142,196 study participants, 95% drank coffee, 64% drank tea, 53% drank caffeinated coffee and 23% drank decaffeinated coffee. The highest median consumption of coffee was reported in Denmark (900 ml/day) and the lowest in Italy (91 ml/day). For caffeinated coffee, the highest and lowest median intakes were reported in the Netherlands (542 ml/day) and Spain (2 ml/day), respectively. The highest and lowest median intakes of decaffeinated coffee were reported in The Netherlands (75 ml/day) and Greece (0.5 ml/day), respectively. The highest median consumption of tea was observed in the UK (475 ml/day) and the lowest in Greece (0.5 ml/day).

The age and country-adjusted baseline characteristics of the men by categories of coffee and tea intake are presented in **Table 1**. Participants consuming higher volumes of coffee were slightly younger, more likely to have a paid employment,

more often current smokers, less physically active, reported more total energy intake and consumed more red and processed meat, but less fish, fruits and vegetables. Participants in the highest tertile of tea consumption were more likely to be educated, less likely to smoke and to have diabetes, reported a lower total energy intake and consumed less alcohol, red and processed meat, fish, fruits and vegetables.

In multivariable Cox models, we observed no association between total coffee intake and risk of total prostate cancer comparing highest to lowest consumers (HR, 1.02; 95% CI, 0.94-1.09) (**Table 2**). The HR associated with a linear increase in coffee consumption per 200 ml/day was 1.00 (95% CI, 0.98 -1.01). Similarly, we observed no association between tea intake and total prostate cancer risk (highest vs. lowest consumers: HR, 0.98; 95% CI, 0.90 – 1.07) (**Table 3)**. Consumption of caffeinated or decaffeinated coffee was also not associated with total prostate cancer risk (**Tables 4 and 5**). Non-consumers of coffee and tea were at a similar risk for total prostate cancer risk compared with consumers in the lowest category of coffee and tea consumption. Moreover, we found no associations of coffee and tea consumption for subtypes of prostate cancer risk defined according to stage, grade or fatality (**Table 2-5**). There was no evidence of heterogeneity for associations by stage and grade of prostate cancer (all P-values > 0.10). No evidence was observed for any non-linear association (data not shown).

We also found no clear evidence for any multiplicative interaction by age at recruitment, smoking status, obesity and physical activity (**Table 6**). When analyses were performed by EPIC-participating country, all associations were null and there was no between-country heterogeneity (**Table 6**). In sensitivity analyses, when 279 prostate cancer cases diagnosed within the first 2 years of follow-up were excluded, or after additional adjustment for a more detailed list of potential confounders, or after

considering non-consumers as the reference group, all results were very similar (data not shown).

DISCUSSION

In this large prospective multi-center cohort study of 142,196 men, of whom 7,036 were diagnosed with prostate cancer during 14 years of follow-up, we found no evidence of an association between coffee or tea consumption and risk of total prostate cancer. Likewise, null associations were observed for caffeinated and decaffeinated coffee consumption and for associations by prostate cancer grade, stage, fatality, or according to age, BMI, smoking status and physical activity.

Findings from previous studies on total coffee consumption and risk of total prostate cancer have been inconsistent with most, though not all studies, reporting null results [8, 12-15, 19]. The meta-analysis of eight cohort studies conducted by the World Cancer Research Fund (WCRF) Continuous Update Project (CUP) in 2014 revealed a summary relative risk (RR) of 0.99 (95% CI, 0.98-1.00) per 1 cup/day [7], which was in agreement with findings in the current study. Critical appraisals of the literature have categorized the association between coffee and prostate cancer risk under limited or weak evidence [8, 19]. Other more recent and slightly larger meta-analyses reported either similar null findings (13 cohorts; RR, 0.98; 95% CI, 0.96-1.00) or weak inverse results (14 cohorts; RR, 0.97; 95% CI, 0.96-0.98) per 2 cups of total coffee per day [13, 14]. A recently published Mendelian randomization study observed no association between genetically predicted coffee consumption and prostate cancer incidence or progression [20].

Prostate cancer is a heterogeneous disease and conducting investigations by stage, grade or fatality are important for identifying associations specific for fatal

tumours or tumours that are likely to advance to metastatic disease. Unfortunately, less than half of the available cohort studies have investigated such associations [7, 21-24]. Total coffee consumption (per 1 cup/day) was not associated with risk of fatal prostate cancer in the WCRF-CUP meta-analysis (4 cohorts; RR, 0.97; 95% CI, 0.93-1.00) [7] or in another meta-analysis (4 cohorts; RR, 0.76; 95% CI, 0.55-1.06) that compared highest to lowest consumption [13], and a similar result was observed for advanced prostate cancer (6 cohorts; RR, 0.82; 95% CI, 0.61-1.10) [13]. In agreement with the meta-analyses and most other published studies [21, 25, 26], the current study also found no association between total coffee consumption with prostate cancer by stage, grade or fatality. A strikingly different result was observed in the Health Professionals Follow-up Study (HPFS), which found a 60% lower risk of lethal prostate cancer among men who drank six or more cups of coffee per day compared to nondrinkers (RR, 0.40; 95% CI, 0.22-0.75) [22].

Study differences may explain the discrepancy between our findings and those in HPFS. In EPIC, we had a narrower range of coffee intakes (inter-quartile range, 139-665 mL/d) compared to HPFS, but other North American or European studies with similar ranges of coffee consumption to HPFS observed null findings for coffee and fatal prostate cancer [7, 21]. When we performed an analysis in EPIC between the 5,018 men, 46 of which develop fatal prostate cancer, who drank six or more cups (approximately 1,418 ml) of coffee per day compared to nondrinkers, the results were null (HR, 1.04; 95% CI, 0.67-1.62). Evidence from experimental studies appears to suggest that coffee and tea, which are major sources of antioxidants, may have an inhibitory effect on carcinogenesis of prostate cancer [10, 27, 28], which could be explained by the fact that very high doses of coffee or tea are used in the laboratory studies but it is also plausible that there is no effect in humans. A total of 642 fatal

cases were included in HPFS, of which only 12 cases drank six or more cups/day; therefore, a future analysis with larger follow-up from HPFS may assist in obtaining a more stable estimate for the top consumption category.

On the contrary, the HPFS has time-updated information on coffee consumption every 4 years, whereas many of the other cohorts, including EPIC, rely only on baseline assessments and are unable to account for dietary changes during follow-up. Such changes could lead to non-differential measurement error in the assessment of coffee consumption, which could bias results towards the null. Diverging findings in different studies might be also owing to the different types of raw coffee and the different concentrations and preparations, as the particle content and dissolved caffeine content may differ [29-33]. We did not identify a differing association by caffeinated or decaffeinated coffee consumption, similar to HPFS and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening study cohort [22, 30], but these and other types of coffee (e.g., type of coffee bean, roasting and brewing methods) should be investigated in greater detail in future studies.

Previous studies investigating the association between tea consumption and risk of prostate cancer have largely produced null results [7, 12, 15]. A recent meta-analysis of 28 cohort and case-control studies reported null relative risks of 0.86 (95% CI, 0.69-1.04), 0.88 (95% CI, 0.73-1.02) and 0.79 (95% CI, 0.43-1.14) comparing highest to lowest consumption of total, black or green tea, respectively [12]. The summary finding in the 9 included cohort studies for total tea intake was also null (RR, 0.98; 95% CI, 0.86-1.09), in agreement with the findings in the current study.

The present study has a number of strengths, including its prospective design that minimizes reverse causation to a large extent, the large number of prostate cancer cases ascertained over a long follow-up period, information on stage, grade and

fatality of prostate cancer, data on caffeinated and decaffeinated coffee as well as rich data on a wide-range of potential confounders. Nonetheless, the study also has some limitations. First, information on coffee and tea intake was self-reported only at recruitment, which will inevitably be imperfect. However, this information in EPIC was shown to be reliable and valid compared to repeat food frequency questionnaires and multiple 24-hour diet recalls [17]. Second, we did not collect information about temperature and type of tea consumption (green, black or other types), although Europeans habitually drink black tea at warm temperature. The potential addition of milk to the tea was also not captured in the questionnaires. Third, the serving size and concentration of coffee and tea consumed are different among countries included in this study, but our results used country-specific cut-off points that may minimize misclassification.

In conclusion, our findings suggest no evidence of association between coffee or tea consumption and risk of prostate cancer. Further investigations are needed to confirm these findings and clarify whether an association exists for different preparations, concentrations and constituents of these beverages.

Conflict of interest: The authors declare no conflict of interest

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Table 1 Country and age-adjusted characteristics at recruitment by coffee or tea intake in EPIC[1]

Characteristics	Fourths of Frequency of observed total coffee consumption (*ml/day*)				
	Non-consumers	1 (Low)	2 (Moderately low)	3 (Moderately high)	4 (High)
Mean age (SD) , year	53.1 (SD=10.7)	52.7 (SD=10.7)	53.0 (SD=9.6)	50.5 (SD=9.9)	49.7 (SD=9.5)
University graduate (95% CI),%	23.7 (22.7 – 24.8)	27.7 (27.3 – 28.2)	26.3 (25.8 – 26.8)	27.5 (27.0 – 28.0)	25.9 (25.4 – 26.5)
Current Smoker (95% CI), %	18.6 (17.7 – 19.6)	21.8 (21.4 – 22.3)	26.0 (25.6 – 26.5)	33.5 (33.0 – 34.0)	43.1 (42.5 – 43.6)
Employed (95% CI), %	75.6 (74.3 – 76.8)	78.9 (78.4 – 79.3)	81.0 (80.6 – 81.6)	81 (81 – 82)	83 (83 – 84)
Physically active (95% CI), %	50.4 (49.2 – 51.6)	50.8 (50.3 – 51.3)	50.8 (50.2 – 51.3)	48.6 (48.0 – 49.1)	23 (22 – 23)
Mean body mass index (95% CI), %	26.7 (26.6 – 26.8)	26.5 (26.5 – 26.6)	26.5 (26.4 – 26.5)	26.7(26.6 – 26.7)	26.8 (26.7 – 26.8)
Diabetes (95% CI),%	36.1 (32.1 – 40.6)	29.8 (28.2– 31.5)	30.1 (28.4 – 32.0)	26.4 (24.7 – 28.2)	35.9 (33.8 – 38.2)
Daily mean (95% CI) dietary intake					
Energy, kcal	2355 (2340 – 2371)	2343 (2336 – 2349)	2368 (2362 – 2375)	2448 (2441 – 2456)	2524 (2517 – 2532)
Alcohol, g	17.4 (16.9 – 18.0)	21.6 (21.4 – 21.8)	20.9 (20.7 – 21.1)	20.9 (20.6 – 21.1)	20.2 (19.9 – 20.4)
Fruits and vegetables, g	435.1 (429.2 – 441.0)	435.4 (432.9 – 438.0)	376.3 (373.7 – 379.0)	395.9 (393.0 – 398.7)	378.9 (375.9 – 381.8)
Red and processed meat, g	54.1 (53.2 – 55.0)	55.5 (55.1 – 55.9)	55.6 (55.2 – 56.0)	54.4 (54.0 – 54.9)	56.1 (55.6 – 56.5)
Fish, g	33.3 (32.7 – 34.0)	28.2 (27.9 – 28.5)	28.0 (27.7 – 28.3)	25.7 (25.4 – 26.0)	26.5 (26.2 – 26.9)
Calcium, mg	1050 (1042 – 1058)	1044 (1041– 1048)	1041 (1037 – 1044)	1033 (1029 – 1037)	1052 (1048 - 1056)

	Thirds of Frequency of observed tea consumption (*ml/day*)			
	Non-consumers	1 (Low)	2 (Moderate)	3 (High)
Mean age (SD), year	53.5 (SD=8.7)	50.1 (SD=11.4)	51.3 (SD=10.2)	50.9 (SD=10.2)
University graduate (95% CI),%	18.4 (18.0 – 18.7)	31.0 (30.5 – 31.5)	30.4 (29.9 – 30.9)	34.2 (33.5 – 34.8)
Current Smoker (95% CI), %	38.4 (37.9 – 38.8)	27.0 (26.5 – 27.4)	24.6 (24.1 – 25.1)	21.7 (21.1 – 22.3)
Employed (95% CI),%	79.5 (79.1 – 79.9)	80.8 (80.3 – 81.2)	82.2 (81.7 – 82.6)	81.1 (80.6 – 81.7)
Physically active (95% CI), %	48.9 (48.5 – 49.4)	48.0 (47.5 – 48.5)	52.0 (51.5 – 52.6)	49.6 (48.9 – 52.6)
Mean body mass index (95% CI), %	27.1 (27.1 – 27.2)	26.2 (26.1 – 26.3)	26.2 (26.1 – 26.3)	25.9 (25.8 – 25.9)
Diabetes (95% CI),%	34.5 (32.9 – 36.1)	27.2 (25.5 – 29.0)	28.5 (26.7 – 30.4)	18.8 (27.5 – 32.1)
Daily mean (95% CI) dietary intake[1]				
Energy, kcal	2500 (2494 – 2506)	2278 (2272 – 2285)	2426 (2419 – 2433)	2412 (2403 – 2420)
Alcohol, g	23.4 (23.2 – 23.6)	20.3 (20.1 – 20.5)	19.7 (19.4 – 19.9)	17.4 (17.1 – 17.7)
Fruits and vegetables, g	416 (414 – 418)	410 (408 – 413)	384 (381 – 387)	369 (365 – 372)

Red and processed meat, g	58.9 (58.5 – 59.2)	52.3 (51.9 – 52.7)	58.0 (57.5 – 58.4)	48.7 (48.2 – 49.2)
Fish, g	34.0 (33.7 – 34.2)	23.4 (23.1 – 23.7)	26.2 (25.9 – 26.5)	21.8 (21.5 – 22.2)
Calcium, mg	985 (982 – 988)	1075 (1071 – 1078)	1075 (1071 – 1078)	1075 (1070 – 1079)

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition, CI, confidence interval, SD, Standard deviation

[1] Age at recruitment-adjusted means and proportions are presented using linear and logistic regression models, respectively. The means of dietary intake are also adjusted for daily energy intake and EPIC center.

Table 2 Hazard ratio (HR) and 95% confidence interval (CI) for the association between total coffee intake and risk of total prostate cancer and cancer by stage, grade and fatality

Characteristics	Fourths of observed total coffee intake[1]					
	Non-consumer N= 7,161	1 (Low) N= 39,007	2 (Moderately low) N= 35,691	3 (Moderately High) N= 30,690	4 (High) N= 29,647	Per 200 ml N= 135,035
Median coffee intake (ml /day)	0	103	376	500	855	
All prostate cancer (No. of cases)	*369*	*1,996*	*1,962*	*1,438*	*1,271*	*6,667*
Crude HR (95% CI)[2]	1.07 (0.96 – 1.20)	1.00 (ref)	1.02 (0.96 – 1.09)	0.99 (0.93 – 1.07)	0.99 (0.82 – 1.05)	0.99 (0.98 - 1.01)
Multivariable adjusted HR (95% CI)[3]	1.07 (0.95 – 1.19)	1.00 (ref)	1.03 (0.97 – 1.10)	1.02 (0.95 – 1.09)	1.02 (0.94 – 1.09)	1.00 (0.98 –1.01)
Localized prostate cancer[4] (No. of cases)	*141*	*673*	*857*	*536*	*434*	*2,500*
Crude HR (95% CI)[2]	0.99 (0.82 – 1.19)	1.00 (ref)	1.06 (0.95 – 1.18)	1.00 (0.89 – 1.12)	0.99 (0.87 -- 1.11)	0.98 (0.96 – 1.01)
Multivariable adjusted HR (95% CI)[3]	0.97 (0.81 – 1.17)	1.00 (ref)	1.07 (0.96 – 1.19)	1.02 (0.91 – 1.15)	1.02 (0.90 – 1.16)	0.99 (0.96 – 1.02)
Advanced prostate cancer[5] (No. of cases)	*68*	*400*	*395*	*277*	*249*	*1,321*
Crude HR (95% CI)[2]	1.14 (0.87 – 1.48)	1.00 (ref)	1.00 (0.87 – 1.16)	1.04 (0.89 – 1.21)	1.11 (0.95 – 1.31)	1.03 (1.00 – 1.06)
Multivariable adjusted HR (95% CI)[3]	1.16 (0.89 – 1.51)	1.00 (ref)	0.99 (0.85 – 1.14)	1.01 (0.86 – 1.19)	1.09 (0.92 – 1.29)	1.02 (0.99 – 1.06)
Low-grade prostate cancer[6] (No. of cases)	*214*	*967*	*1119*	*766*	*691*	*3,543*
Crude HR (95% CI)[2]	1.07 (0.92 – 1.24)	1.00 (ref)	1.05 (0.96 – 1.14)	1.00 (0.91 – 1.10)	1.05 (0.95 – 1.16)	0.99 (0.98 – 1.02)
Multivariable adjusted HR (95% CI)[3]	1.05 (0.90 – 1.23)	1.00 (ref)	1.06 (0.97 – 1.16)	1.02 (0.93 – 1.13)	1.09 (0.98 – 1.21)	1.01 (0.99 – 1.03)
High-grade prostate cancer[7] (No. of cases)	*36*	*200*	*240*	*138*	*112*	*690*
Crude HR (95% CI)[2]	0.99 (0.69 – 1.42)	1.00 (ref)	1.08 (0.89 – 1.31)	1.00 (0.80 – 1.25)	0.95 (0.75 – 1.20)	1.01 (0.96 – 1.05)
Multivariable adjusted HR (95% CI)[3]	0.99 (0.69 – 1.43)	1.00 (ref)	1.09 (0.90 – 1.33)	1.01 (0.81 – 1.27)	0.97 (0.76 – 1.25)	1.01 (0.97 – 1.06)
Aggressive prostate cancer[8] (No. of cases)	*97*	*611*	*672*	*412*	*363*	*2,058*
Crude HR (95% CI)[2]	0.97 (0.78 – 1.21)	1.00 (ref)	1.07 (0.95 – 1.19)	1.00 (0.88 – 1.13)	1.06 (0.93 – 1.21)	1.01 (0.99 – 1.03)
Multivariable adjusted HR (95% CI)[3]	0.98 (0.78 – 1.22)	1.00 (ref)	1.07 (0.95 – 1.20)	1.00 (0.88 – 1.14)	1.07 (0.93 – 1.23)	1.01 (0.99 – 1.04)
Fatal prostate cancer (No. of cases)	*46*	*279*	*283*	*186*	*142*	*890*
Crude HR (95% CI)[2]	1.01 (0.73 – 1.40)	1.00 (ref)	1.07 (0.90 – 1.27)	1.11 (0.92 – 1.33)	1.03 (0.83 – 1.26)	0.99 (0.95 – 1.03)
Multivariable adjusted HR (95% CI)[3]	1.02 (0.74 – 1.41)	1.00 (ref)	1.05 (0.88 – 1.25)	1.06 (0.88 – 1.29)	0.97 (0.79 – 1.21)	0.97 (0.93 – 1.01)

[1] Cut-off points are based on country–specific quartiles of total coffee intake after exclusion of non-consumers: Total cohort (136, 376, 654), Italy (60, 91, 131), Spain (49, 100, 161), UK (151,475, 502), The Netherlands (375, 625, 875), Greece (140, 170, 310), Germany (261, 428, 580), Sweden (321, 443, 610), Denmark (500, 900, 1300).

[2] Stratified by center, and age at recruitment in 5yr categories.

[3] Stratified by center, and age at recruitment in 5yr categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, as well as calcium, fish, tea, fruit and vegetable intake.

[4] Tumor-node-metastasis staging score of T0-T2 and N0/NX and M0, or stage coded in the recruitment center as localized.

[5] T3-T4 and/or N1-N3 and/or M1, or stage coded in the recruitment center as metastatic.

[6] Gleason score of <8, or grade coded as well, moderately or poorly differentiated.

[7] Gleason score of ≥8, or grade coded as undifferentiated.

[8] High-grade or advanced disease or PSA>20 ng/mL at diagnosis

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) for the association between tea intake and risk of total prostate cancer and cancer by stage, grade and fatality

	Thirds of observed tea intake[1]				
	Non consumer N= 50,140	1 (Low) N= 37,582	2 (Moderate) N= 32,185	3 (High) N= 21,289	Per 100 ml/L N= 91,056
Median tea intake (ml /day)	0	12	119	450	
All prostate cancer (No. of cases)	*2,792*	*1,624*	*1,647*	*973*	*4,244*
Crude HR (95% CI)[2]	0.91 (0.84 - 0.99)	1.00 (ref)	0.99 (0.92 – 1.06)	1.00 (0.92 – 1.09)	1.00 (0.99 – 1.01)
Multivariable adjusted HR (95% CI)[3]	0.93 (0.85 – 1.01)	1.00 (ref)	0.98 (0.91 – 1.05)	0.98 (0.90 – 1.07)	1.00 (0.99 – 1.01)
Localized prostate cancer[4] (No. of cases)	*923*	*642*	*633*	*443*	*1,108*
Crude HR (95% CI)[2]	0.85 (0.74 – 0.98)	1.00 (ref)	0.96 (0.86 – 1.07)	0.96 (0.85 – 1.09)	1.00 (0.98 – 1.01)
Multivariable adjusted HR (95% CI)[3]	0.87 (0.76 – 1.00)	1.00 (ref)	0.94 (0.84 – 1.06)	0.93 (0.82 – 1.06)	0.99 (0.98 – 1.01)
Advanced prostate cancer[5] (No. of cases)	*443*	*364*	*373*	*209*	*946*
Crude HR (95% CI)[2]	1.03 (0.87 – 1.21)	1.00 (ref)	0.92 (0.79 – 1.06)	0.97 (0.82 – 1.16)	0.99 (0.97 – 1.01)
Multivariable adjusted HR (95% CI)[3]	1.01 (0.86 – 1.20)	1.00 (ref)	0.94 (0.81 – 1.09)	1.01 (0.85 – 1.21)	1.00 (0.98 – 1.02)
Low-grade prostate cancer[6] (No. of cases)	*1301*	*961*	*862*	*633*	*2,456*
Crude HR (95% CI)[2]	0.86 (0.77 – 0.96)	1.00 (ref)	0.94 (0.86 – 1.04)	1.00 (0.90 – 1.10)	1.00 (0.99 – 1.01)
Multivariable adjusted HR (95% CI)[3]	0.88 (0.78 – 0.98)	1.00 (ref)	0.94 (0.85 – 1.03)	0.99 (0.89 – 1.10)	1.00 (0.98 – 1.01)
High-grade prostate cancer[7] (No. of cases)	*211*	*192*	*210*	*113*	*515*
Crude HR (95% CI)[2]	0.99 (0.77 – 1.28)	1.00 (ref)	1.10 (0.90 – 1.35)	1.07 (0.84 – 1.36)	0.98 (0.96 – 1.04)
Multivariable adjusted HR (95% CI)[3]	0.98 (0.76 – 1.27)	1.00 (ref)	1.11 (0.90 – 1.36)	1.09 (0.86 – 1.40)	1.01 (0.99 – 1.04)
Aggressive prostate cancer[8] (No. of cases)	*687*	*539*	*609*	*320*	*1,468*
Crude HR (95% CI)[2]	1.06 (0.92 – 1.23)	1.00 (ref)	1.07 (0.95 – 1.20)	1.04 (0.84 – 1.26)	1.00 (0.99 – 1.02)
Multivariable adjusted HR (95% CI)[3]	1.05 (0.91 – 1.22)	1.00 (ref)	1.08 (0.96 – 1.22)	1.06 (0.92 – 1.23)	1.00 (0.99 – 1.02)
Fatal prostate cancer (No. of cases)	*348*	*239*	*239*	*110*	*588*
Crude HR (95% CI)[2]	0.95 (0.75 – 1.20)	1.00 (ref)	0.99 (0.82 – 1.19)	0.92 (0.73 – 1.15)	0.99 (0.96 – 1.01)
Multivariable adjusted HR (95% CI)[3]	0.93 (0.74 – 1.18)	1.00 (ref)	0.97 (0.81 – 1.17)	0.89 (0.70 – 1.13)	0.98 (0.96 – 1.01)

[1] Cut-off points are based on country–specific tertiles of tea intake after exclusion of non-consumers: Total cohort (25, 281), Italy (10, 43), Spain (57, 171), UK (475, 855), The Netherlands (74, 238), Greece (0.5, 11), Germany (21, 145), Sweden (16, 179) and Denmark (16, 500).

[2] Stratified by center, and age at recruitment in 5yr categories.

[3] Stratified by center, and age at recruitment in 5yr categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, as well as calcium, fish, coffee, fruit and vegetable intake.

[4] Tumor-node-metastasis staging score of T0-T2 and N0/NX and M0, or stage coded in the recruitment center as localized.

[5] T3-T4 and/or N1-N3 and/or M1, or stage coded in the recruitment center as metastatic.

[6] Gleason score of <8, or grade coded as well, moderately or poorly differentiated.[7] Gleason score of ≥8, or grade coded as undifferentiated.

[8] High-grade or advanced disease or PSA>20 ng/mL at diagnosis

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) for the association between caffeinated coffee intake and risk of total prostate cancer and cancer by stage, grade and fatality

	Thirds of observed caffeinated coffee intake[1]				
	Non consumer N= 25,064	1 (Low) N= 31,350	2 (Moderate) N= 23,860	3 (High) N= 20,773	Per 100 ml/L N= 75,983
Median caffeinated coffee intake (ml /day)	0	81	475	787	
All prostate cancer (No of cases)	*994*	*1,459*	*1,154*	*838*	*3,451*
Crude HR (95% CI)[2]	0.96 (0.85 – 1.08)	1.00 (ref)	1.02 (0.94 – 1.10)	0.95 (0.87 – 1.04)	0.99 (0.98 – 1.00)
Multivariable adjusted HR (95% CI)[3]	0.97 (0.86 – 1.09)	1.00 (ref)	1.02 (0.94 – 1.10)	0.98 (0.89 – 1.07)	1.00 (0.99 – 1.01)
Localized prostate cancer[4] (No of cases)	*529*	*423*	*311*	*257*	*991*
Crude HR (95% CI)[2]	0.87 (0.72 – 1.06)	1.00 (ref)	1.00 (0.86 – 1.16)	1.00 (0.85 – 1.17)	0.99 (0.97 – 1.01)
Multivariable adjusted HR (95% CI)[3]	0.89 (0.73 – 1.08)	1.00 (ref)	1.01 (0.87 – 1.17)	1.03 (0.88 – 1.21)	1.00 (0.98 – 1.02)
Advanced prostate cancer[5] (No of cases)	*146*	*258*	*196*	*135*	*589*
Crude HR (95% CI)[2]	0.96 (0.73 – 1.25)	1.00 (ref)	0.98 (0.81 – 1.18)	0.97 (0.78 – 1.20)	1.00 (0.98 – 1.03)
Multivariable adjusted HR (95% CI)[3]	0.97 (0.74 – 1.28)	1.00 (ref)	0.98 (0.81 – 1.18)	0.96 (0.78 – 1.20)	1.00 (0.98 – 1.03)
Low-grade prostate cancer[6] (No of cases)	*707*	*815*	*593*	*459*	*1,867*
Crude HR (95% CI)[2]	0.93 (0.80 – 1.09)	1.00 (ref)	0.99 (0.89 – 1.10)	0.99 (0.88 – 1.18)	1.00 (0.99 – 1.02)
Multivariable adjusted HR (95% CI)[3]	0.94 (0.81 – 1.10)	1.00 (ref)	1.00 (0.90 – 1.12)	1.02 (0.91 – 1.15)	1.01 (0.99 – 1.02)
High-grade prostate cancer[7] (No of cases)	*101*	*141*	*103*	*54*	*298*
Crude HR (95% CI)[2]	0.75 (0.51 – 1.11)	1.00 (ref)	1.01 (0.78 – 1.30)	0.84 (0.61 – 1.15)	0.98 (0.94 – 1.02)
Multivariable adjusted HR (95% CI)[3]	0.75 (0.50 – 1.11)	1.00 (ref)	1.00 (0.77 – 1.30)	0.83 (0.60 – 1.15)	0.98 (0.94 – 1.02)
Aggressive prostate cancer[8] (No of cases)	*279*	*394*	*296*	*190*	*880*
Crude HR (95% CI)[2]	0.94 (0.75 – 1.17)	1.00 (ref)	1.00 (0.86 – 1.17)	0.96 (0.80 – 1.14)	1.00 (0.98 – 1.02)
Multivariable adjusted HR (95% CI)[3]	0.94 (0.75 – 1.18)	1.00 (ref)	1.01 (0.86 – 1.17)	0.96 (0.80 – 1.15)	1.00 (0.98 – 1.03)
Fatal prostate cancer (No of cases)	*114*	*193*	*160*	*93*	*446*
Crude HR (95% CI)[2]	0.93 (0.67 – 1.29)	1.00 (ref)	1.10 (0.89 – 1.36)	1.20 (0.93 – 1.55)	1.02 (0.99 – 1.05)
Multivariable adjusted HR (95% CI)[3]	0.97 (0.70 – 1.34)	1.00 (ref)	1.08 (0.87 – 1.34)	1.16 (0.89 – 1.51)	1.01 (0.98 – 1.04)

[1] Cut-off points are based on country–specific tertiles of caffeinated coffee intake after exclusion of non-consumers: Total cohort (150, 475), Italy (60, 104), Spain (2.0, 3.0), UK (190, 475), The Netherlands (360, 675), Greece (79, 170), Germany (290, 523), Sweden (343, 600).

[2] Stratified by center, and age at recruitment in 5yr categories.

[3] Stratified by center, age at recruitment in 5yr categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, and calcium, fish, decaffeinated coffee, tea, fruit and vegetable.

[4] Tumor-node-metastasis staging score of T0-T2 and N0/NX and M0, or stage coded in the recruitment center as localized.

[5] T3-T4 and/or N1-N3 and/or M1, or stage coded in the recruitment center as metastatic.

[6] Gleason score of <8, or grade coded as well, moderately or poorly differentiated.[7] Gleason score of ≥8, or grade coded as undifferentiated.

[8] High-grade or advanced disease or PSA>20 ng/mL at diagnosis

Table 5 Hazard ratio (HR) and 95% confidence interval (CI) for the association between decaffeinated coffee intake and risk of total prostate cancer and cancer by stage, grade and fatality

	Thirds of observed decaffeinated coffee intake[1]				
	Non-consumer N= 57,655	1 (Low) N= 16,039	2 (Moderate) N= 6,636	3 (High) N= 10,453	*Per 50 ml* N= 33,128
Median decaffeinated coffee intake (ml /day)	0	2	75	190	
All prostate cancer (No. of cases)	*2,145*	*521*	*200*	*388*	*1,109*
Crude HR (95% CI)[2]	0.99 (0.87 – 1.13)	1.00 (ref)	0.91 (0.77 – 1.08)	0.99 (0.86 – 1.14)	1.00 (0.98 – 1.01)
Multivariable adjusted HR (95% CI)[3]	1.00 (0.87 – 1.14)	1.00 (ref)	0.92 (0.77 – 1.09)	1.00 (0.87 – 1.15)	1.00 (0.98 – 1.01)
Localized prostate cancer[4] (No. of cases)	*1,034*	*120*	*59*	*130*	*309*
Crude HR (95% CI)[2]	0.90 (0.73 – 1.11)	1.00 (ref)	0.66 (0.48 – 0.90)	0.91 (0.70 – 1.18)	1.02 (0.99 – 1.04)
Multivariable adjusted HR (95% CI)[3]	0.92 (0.75 – 1.13)	1.00 (ref)	0.67 (0.48 – 0.92)	0.93 (0.72 – 1.20)	1.02 (0.99 – 1.04)
Advanced prostate cancer[5] (No. of cases)	*393*	*105*	*52*	*79*	*236*
Crude HR (95% CI)[2]	0.88 (0.66 – 1.19)	1.00 (ref)	0.91 (0.64 – 1.29)	0.88 (0.64 – 1.20)	0.98 (0.95 – 1.02)
Multivariable adjusted HR (95% CI)[3]	0.88 (0.65 – 1.19)	1.00 (ref)	0.91 (0.64 – 1.29)	0.87 (0.64 – 1.19)	0.98 (0.95 – 1.02)
Low-grade prostate cancer[6] (No. of cases)	*1,552*	*351*	*157*	*268*	*776*
Crude HR (95% CI)[2]	1.02 (0.87 – 1.19)	1.00 (ref)	0.95 (0.77 – 1.15)	1.01 (0.85 – 1.19)	1.00 (0.98 – 1.02)
Multivariable adjusted HR (95% CI)[3]	1.03 (0.88 – 1.20)	1.00 (ref)	0.95 (0.78 – 1.16)	1.02 (0.86 – 1.21)	1.00 (0.98 – 1.02)
High-grade prostate cancer[7] (No. of cases)	*222*	*77*	*15*	*51*	*143*
Crude HR (95% CI)[2]	0.77 (0.53 – 1.11)	1.00 (ref)	0.52 (0.29 – 0.93)	0.84 (0.57 – 1.24)	1.01 (0.97 – 1.05)
Multivariable adjusted HR (95% CI)[3]	0.76 (0.52 – 1.11)	1.00 (ref)	0.52 (0.29 – 0.93)	0.83 (0.56 – 1.24)	1.00 (0.97 – 1.05)
Aggressive prostate cancer[8] (No. of cases)	*609*	*186*	*75*	*133*	*394*
Crude HR (95% CI)[2]	0.84 (0.67 – 1.06)	1.00 (ref)	0.92 (0.69 – 1.22)	0.91 (0.71 – 1.15)	0.99 (0.96 – 1.02)
Multivariable adjusted HR (95% CI)[3]	0.84 (0.67 – 1.06)	1.00 (ref)	0.92 (0.69 – 1.23)	0.90 (0.71 – 1.15)	0.99 (0.96 – 1.01)
Fatal prostate cancer (No. of cases)	*242*	*79*	*24*	*45*	*148*
Crude HR (95% CI)[2]	1.20 (0.80 – 1.81)	1.00 (ref)	1.08 (0.66 – 1.78)	0.83 (0.56 – 1.24)	0.95 (0.90 – 1.00)
Multivariable adjusted HR (95% CI)[3]	1.19 (0.79 – 1.80)	1.00 (ref)	1.07 (0.65 – 1.77)	0.85 (0.57 – 1.28)	0.95 (0.90 – 1.00)

[1] Cut-off points are based on country–specific tertiles of decaffeinated coffee intake after exclusion of non-consumers: Total cohort (2.2, 75), Italy (6.4, 20), Spain (2.0, 3.0), UK (2.0, 27), The Netherlands (63, 100) Greece (0.5, 11), Germany (19, 150).

[2] Stratified by center, and age at recruitment in 5 categories.

[3] Stratified by center, age at recruitment in 5 categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, as well as calcium, fish, caffeinated coffee, tea, fruit and vegetable.

[4] Tumor-node-metastasis staging score of T0-T2 and N0/NX and M0, or stage coded in the recruitment center as localized.

[5] T3-T4 and/or N1-N3 and/or M1, or stage coded in the recruitment center as metastatic.

[6] Gleason score of <8, or grade coded as well, moderately or poorly differentiated.[7] Gleason score of ≥8, or grade coded as undifferentiated.

[8] High-grade or advanced disease or PSA>20 ng/mL at diagnosis.

Table 6 Hazard ratio (HR) and 95% confidence interval (CI) for the association of continuous total coffee (200ml/day only among consumers) and tea (100ml/day only among consumers) consumption and prostate cancer risk by country and other baseline characteristics

	Total coffee intake		Tea intake	
	Cases/Control	HR (95% CI)[2]	Cases/Control	HR (95% CI)[2]
Country[1]				
Denmark	1,832/ 23,776	0.99 (0.97 – 1.01)	1503/ 19015	1.00 (0.98 -- 1.01)
Germany	796/ 19,386	0.98 (0.94 – 1.02)	619/ 15247	1.03 (1.00 -- 1.06)
Greece	88/ 10,222	0.90 (0.65 – 1.25)	50/ 5850	1.14 (0.68 – 1.91)
Italy	479/13,553	0.89 (0.64 – 1.24)	254/ 7453	0.99 (0.87 – 1.14)
Spain	581/ 12,666	1.01 (0.85 – 1.20)	23/ 472	0.87 (0.63 – 1.22)
Sweden	1,767/ 19,769	0.99 (0.96 – 1.02)	616/ 10872	0.98 (0.93 – 1.02)
The Netherland	213/ 8,974	1.01 (0.93 – 1.09)	178/ 7870	1.01 (0.95 – 1.08)
UK	942/ 20,646	1.00 (0.96 – 1.04)	1001/ 21033	1.00 (0.98 – 1.02)
P-heterogeneity, I^2		0.98, 0.0%		0.61, 0.0%
Baseline Age				
< 60y	4,007/100,262	0.99 (0.97 – 1.01)	2582/ 69478	0.99 (0.98 – 1.01)
≥ 60y	2,660/ 28,664	1.01 (0.99 – 1.04)	1662/ 18334	1.01 (0.99 – 1.02)
P-interaction		0.22		0.48
BMI				
<30 Kg/m^2	5,782/ 108,695	1.00 (0.98 – 1.01)	3767/ 76628	1.00 (0.99 – 1.01)
≥30 Kg/m^2	885/ 19,673	1.00 (0.96 – 1.04)	477/ 11184	1.01 (0.98 – 1.05)
P-interaction		0.70		0.50
<25 Kg/m^2	2,359/ 46,269	0.99 (0.97 – 1.01)	1603/ 35744	0.99 (0.98 – 1.01)
≥25 Kg/m^2	4,308/ 82,099	1.00 (0.98 – 1.02)	2641/ 52068	1.00 (0.99 – 1.02)
P-interaction		0.97		0.36
Smoking Status				
Never Smoker	2,259/ 41,499	1.01 (0.98 – 1.04)	1551/ 32084	1.01 (0.99 – 1.02)
Ever smoker	4,353/ 85,121	0.99 (0.97 – 1.01)	2640/ 54267	1.00 (0.98 – 1.01)
P-interaction		0.62		0.66
Physical Activity				
Inactive	3,520/ 63,109	1.00 (0.98 – 1.03)	2166/ 41765	1.00 (0.99 – 1.02)
Active	3,054/ 62,463	0.99 (0.97 – 1.01)	1994/ 43524	1.00 (0.99 – 1.01)
P-interaction		0.36		0.81

[1] Coffee and tea information was missing for participants from Norway, France as well as n=1,828 participants from UK.
[2] From Cox proportional hazard models stratified by center and age at recruitment.

Supplemental Table 1 Cohort and participant characteristics at recruitment in EPIC by country

	All		Denmark		Germany		Greece		Italy		The Netherlands		Spain		Sweden		UK	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Cohort Size	142,196		26,294		21,177		10,813		14,032		9,625		15,128		22,306		22,821	
Mean Age, y	51.7		56.1		51.9		52.3		49.7		42.7		50.2		51.4		52.4	
Prostate cancer, n																		
Total	7036		1885		833		97		479		215		666		1833		1028	
Stage																		
Localized	2641		540		533		35		93		32		423		733		252	
Advanced	1389		550		186		21		92		74		74		192		200	
Missing	3006		795		114		41		294		109		169		908		576	
Grade																		
Low grade	3757		652		687		53		334		189		527		722		593	
High grade	726		240		68		2		46		17		77		113		163	
Missing	2553		993		78		42		99		9		62		998		272	
Aggressive[1]	2155		769		253		22		122		86		183		357		363	
Fatal	936		312		45		22		33		22		61		224		217	
Fourths of observed total coffee intake[2]																		
Non consumer	7,161	5.0	686	2.6	995	4.7	503	4.7	655	4.7	438	4.5	1,881	12.4	770	3.5	1,233	5.4
1 (Low)	39,007	27.0	9,333	35.5	5,189	24.5	4,317	39.9	3,462	24.7	2,318	24.1	3,337	22.0	5,449	24.4	5,602	21.7
2 (Moderately low)	35,691	25.6	7,607	28.9	4,943	23.3	856	7.9	3,256	23.2	2,553	26.5	3,849	25.5	5,340	27.1	7,287	31.7

3 (Moderately high)	30,690	20.6	5,049	19.2	5,106	24.1	2,770	25.3	3,331	23.8	2,315	24.0	2,770	18.3	5,938	23.5	3,444	11.8
4 (High)	29,647	20.6	3,619	13.8	4,944	23.4	2,400	22.2	3,328	23.7	2,001	20.8	3,291	21.8	4,809	21.6	5,255	21.3
Median (IQR), ml/day	375 (139 - 665)		900 (500 – 1300)		420 (261 – 580)		171 (140 – 310)		91 (60 – 131)		625 (375 – 875)		100 (48 – 161)		428 (304 – 609)		475 (150 – 502)	
Thirds of observed Tea intake[3]																		
Non- consumer	50,140	35.3	5,776	22.0	5,311	25.0	4,913	45.5	6,325	45.1	1,577	16.4	14,633	96.7	10,818	48.5	787	3.5
1 (Low)	37,582	26.4	6,920	26.3	5,313	25.1	3,708	34.3	2,787	19.9	2,787	27.9	177	1.2	4,353	19.5	12,644	50.5
2 (Moderate)	32,185	22.3	10,586	40.3	5,260	24.9	1,179	10.9	2,506	17.9	3,183	33.1	152	1.0	3,651	16.4	5,668	23.0
3 High)	21,289	14.8	3,012	11.5	5,293	25.0	1,013	9.4	2,414	17.2	2,185	22.7	166	1.1	3,484	15.6	3,722	15.0
Median (IQR), ml/day	106 (16 – 475)		86 (16 – 500)		52 (12 – 214)		0.5 (0.5 – 11.3)		21 (10 – 64)		118 (50 – 323)		100 (43 – 200)		36 (16– 250)		475 (190 – 855)	
Thirds of total decaffeinated Coffee[4]																		
Non- consumer	57,655	76.7	NA	NA	16,513	78.0	9,781	90.5	10,259	73.1	439	4.6	12,372	81.8	NA	NA	8,291	36.4
1 (Low)	16,039	10.3	NA	NA	1,565	7.4	639	5.9	338	2.4	3,728	38.7	1,472	9.7	NA	NA	8,297	30.4
2 (Moderate)	6,636	4.9	NA	NA	1,604	7.6	78	0.7	321	2.3	2,729	28.3	412	2.7	NA	NA	1,492	7.9
3 (High)	10,453	6.8	NA	NA	1,495	7.1	315	2.9	301	2.1	2,729	28.4	872	5.8	NA	NA	4,741	17.3
Missing	51,413	1.3	26,294	100	0	0	0	0	2,813	20.0	0	0	0	0	22,306	100	0	0
Median (IQR), ml/day	27 (1.9 – 125)		NA		53 (11 – 285)		0.5 (0.5 – 34)		10 (5.5 – 28)		75 (50 – 125)		2 (1.3 – 4)		NA		1.9 (1.9 – 149)	
Thirds of caffeinated Coffee[5]																		
Non- consumer	25,064	46.6	NA	NA	2,001	9.4	4,896	45.3	777	5.5	438	4.5	14,272	94.3	452	56.0	2,228	9.8
1 (Low)	31,350	21.5	NA	NA	7,627	36.0	2,223	20.6	4,293	30.6	3,056	32.0	501	3.3	3,282	15.0	10,368	41.7
2 (Moderate)	23,860	16.3	NA	NA	5,289	24.9	1,743	16.1	2,772	19.8	3,984	41.2	95	0.6	3,421	15.0	6,556	26.1

3 (High)	20,773	14.3	NA	NA	6,260	29.6	1,951	18.0	3,377	24.1	2,147	22.3	260	1.7	3,109	13.9	3,669	14.4
Missing	28,122	1.3	26,294	100	0	0	0	0	2,813	20.0	0	0	0	0	12,042	29.3	0	0
Median (IQR), ml/day	300 (93 – 525)		NA		392 (261 – 580)		170 (34 – 340)		90 (55 – 120)		542 (312 – 675)		2 (2 – 4)		450 (300 – 750)		190 (81 – 475)	

Abbreviation: EPIC = European Prospective Investigation in Cancer and Nutrition; UK = United Kingdom; NA = Not Available; IQR = Interquartile range

[1] High-grade or advanced disease or PSA>20 ng/mL at diagnosis.

[2] Cut-off points are based on country-specific quartiles of total coffee intake after exclusion of non-consumers: Total cohort (136, 376, 654), Italy (60, 91, 131), Spain (49, 100, 161), UK (151,475, 502), The Netherlands (375, 625, 875), Greece (140, 170, 310), Germany (261, 428, 580), Sweden (321, 443, 610), Denmark (500, 900, 1300).

[3] Cut-off points are based on country-specific tertiles of tea intake after exclusion of non-consumers: Total cohort (25, 281), Italy (10, 43), Spain (57, 171), UK (475, 855), The Netherlands (74, 238), Greece (0.5, 11), Germany (21, 145), Sweden (16, 179) and Denmark (16, 500).

[4] Cut-off points are based on country-specific tertiles of decaffeinated coffee intake after exclusion of non-consumers: Total cohort (2.2, 75), Italy (6.4, 20), Spain (2.0, 3.0), UK (2.0, 27), The Netherlands (63, 100) Greece (0.5, 11), Germany (19, 150).

[5] Cut-off points are based on country-specific tertiles of caffeinated coffee intake after exclusion of non-consumers: Total cohort (150, 475), Italy (60, 104), Spain (2.0,3.0), UK (190, 475), The Netherlands (360, 675), Greece (79, 170), Germany (290, 523), Sweden (343, 600).