Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multicentre, prospective cohort study.

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TITLE:

Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multi-centre, prospective cohort study.

SHORT TITLE:

Coffee, tea and hepatocellular carcinoma

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ABBREVIATIONS:

HCC: HepatoCellular Carcinoma

HR: Hazard Ratio

CI: Confidence Intervals

EPIC: European Prospective Investigation into Cancer and nutrition

HBV: Hepatitis B virus

HCV: Hepatitis C Virus

HBsAg: Hepatitis B surface Antigen

LRtest: Likelihood Ratio test

Keywords:

Hepatocellular carcinoma, liver cancer, coffee, tea, EPIC

NOVELTY AND IMPACT OF THE WORK:

In the first multi-centre, European cohort study on the topic, intakes of coffee and, to a lesser extent, tea were associated, in a dose-dependent pattern, with lower HCC risk; there was no evidence that these associations were modified by HBV/HCV positivity status or other HCC risk factors. Taking into account that coffee/tea are almost universal exposures, these results may have important implications for high HCC risk subjects.

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ABSTRACT

Inverse associations of coffee and/or tea in relation to hepatocellular carcinoma (HCC) risk have been consistently identified in studies conducted mostly in Asia where consumption patterns of such beverages differ from Europe. In the European Prospective Investigation into Cancer and nutrition (EPIC), we identified 201 HCC cases among 486,799 men/women, after a median follow-up of 11 years. We calculated adjusted hazard ratios (HR) for HCC incidence in relation to quintiles/categories of coffee/tea intakes. We found that increased coffee and tea intakes were consistently associated with lower HCC risk. The inverse associations were substantial, monotonic and statistically significant. Coffee consumers in the highest compared to the lowest quintile had lower HCC risk by 72% (HR: 0.28; 95% confidence intervals (CI): 0.16 to 0.50, *P*-trend <0.001). The corresponding association of tea with HCC risk was 0.41 (95% CI: 0.22 to 0.78, *P*-trend=0.003). There was no compelling evidence of heterogeneity of these associations across strata of important HCC risk factors, including hepatitis B or hepatitis C status (available in a nested case-control study). The inverse, monotonic associations of coffee intake with HCC were apparent for caffeinated (*P*-trend=0.009), but not decaffeinated (*P*-trend=0.45) coffee for which, however, data were available for a fraction of subjects. Results from this multi-centre, European cohort study strengthen the existing evidence regarding the inverse association between coffee/tea and HCC risk. Given the apparent lack of heterogeneity of these associations by HCC risk factors and that coffee/tea are universal exposures, our results could have important implications for high HCC risk subjects.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 85-95% of primary liver cancer cases.[1] Several risk factors have been identified, but with respect to diet only alcohol, obesity[2] and aflatoxin[3] have been documented. The role of other dietary exposures is still under investigation.[4]

Since 2000, the association of coffee and tea consumption with HCC risk has been investigated in case-control and cohort studies conducted mostly in Asia, where exposure patterns to these beverages differ compared to western countries; two cohort studies on coffee intake were conducted in Europe (Finland)[5,6] and none in the USA. In a major review, the evidence regarding the indicated associations was considered inconclusive.[7] Recent meta-analyses, however, pointed to a statistically significant inverse association of coffee intake with primary liver cancer or HCC,[8] as well as, a suggestive inverse association of tea intake with primary liver cancer.[9] The earlier studies differed in the extent of adjustment for important HCC risk factors. Moreover, coffee and tea were, in general, considered separately, even though they may act as mutual confounders in their respective associations with HCC risk.

In the context of the European Prospective Investigation into Cancer and nutrition (EPIC), we investigated the associations of coffee (overall, caffeinated, decaffeinated) and tea consumption with HCC risk. This is the first cohort study on the topic undertaken in a multi-ethnic European population.

METHODS

Participants

EPIC investigates the role of biological, dietary and lifestyle factors in the aetiology of cancer and other chronic diseases. More than 521,000 apparently healthy men and women, aged 25 to 70 years, were recruited between 1992 and 2000 in 23 centres from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom (UK)). The participants were selected from the general population, except for France (women-members of health insurance plans), Utrecht and Florence (women - breast cancer screening), Naples and Norway (women only), the Oxford cohort (which includes a large proportion of vegetarian volunteers) and subsamples of the Italian and Spanish cohorts (mainly members of blood donor associations). Details of EPIC are given elsewhere.[10]

The study was approved by the Ethical Review Board of the International Agency for Research on Cancer, and by the local Ethics Committees in the participating centres. Participants gave informed consent before enrolment. Procedures were in line with the Helsinki declaration.

Assessment of diet

Dietary intakes over the previous year were assessed at enrolment through validated centre-specific questionnaires which enquired also about cups of coffee and tea

consumption per day, week or month.[11] In some centres, additional information on caffeinated and decaffeinated coffee consumption was obtained (Germany, Greece, Italy (except Ragusa and Naples), Netherlands, and UK). Information on tea consumption was not available in Norway. Data on type of tea were not available. Based on the information collected by the questionnaires, beverage intakes were calculated in each center in ml/day in order to take into account differences in cup sizes by region. Total energy intake was calculated through the EPIC Nutrient-Data-Base.[12]

Assessment of lifestyle, somatometry and medical history

At enrolment, standardized questionnaires were used to record sociodemographic, lifestyle and medical history data. Measurements of weight, height and waist/hip circumferences were undertaken for most participants- in France, Norway and Oxford, self-reported weight and height were recorded for the majority of the participants

Follow-up of study population and case ascertainment

Incident HCC cases and vital status were ascertained in most centres through record linkage with cancer and death registries. In France, Germany and Greece a combination of methods was used including health insurance records, pathology registries and active follow-up through mailed questionnaires/telephone interviews. Reported incident cancers were subsequently verified through pathology reports,

medical records and discharge diagnoses. Cancer incidence was coded according to the International Classification of Diseases-Oncology-2. HCC was defined as C22.0.

Censoring dates for cancer incidence for centres using registry data ranged from December 2004 (Asturias (Spain)) to December 2008 (Turin (Italy), Sweden and Norway). For centres using active follow-up, last contact ranged from July 2005 (France) to June 2010 (Heidelberg (Germany)).

From the 521,330 EPIC participants, we excluded 23,818 with prevalent cancer, 4,383 with insufficient follow-up, 78 cases with metastatic cancer or ineligible information on histology, 6,192 with no dietary and 60 with no lifestyle questionnaires. Eventually, 486,799 participants including 201 incident HCC cases were analysed.

Nested case-control study

Within EPIC, a nested case-control study, using data as of 2006 on 125 HCC cases and 250 matched controls was conducted.[13] For these, serum levels of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV) were determined at the Centre de Biologie République laboratory in Lyon, France. Design and methods of this study have been described elsewhere.[13] Controls were selected from those alive and free of cancer at the time of diagnosis of the case. Matching criteria included study centre, sex, age at the time of blood collection, date and time of day of blood collection. Women were additionally matched by menopausal status and by use of exogenous hormones.

Statistical analysis

The associations of coffee, caffeinated/decaffeinated coffee, and tea intake with HCC risk were investigated through Cox proportional hazard models. Age at exit was the underlying time variable defined as the age of: HCC diagnosis (case); diagnosis of any other incident cancer (censored); death for participants who died without cancer (censored); last follow-up for those alive and with no cancer (censored). Age at recruitment was the entry time. All models were stratified by recruitment age (1-year intervals) and study centre.

Coffee intake was considered in sex-specific quintiles (Q1-Q5). For tea, due to the large number of non-consumers (153,097/450,921, 34%), five categories of intake (C1-C5) were created: non-consumers (C1) and the sex-specific quartiles (C2-C5) among consumers. Both variables were considered categorically and per one-level increments. Norway was excluded from tea analyses, as no relevant data were available. Due to potential between-countries variations in coffee/tea volume and concentration, we also based estimation of quintiles of coffee and categories of tea on sex-and-country specific intakes in order to check the robustness of our findings. Linear trends were evaluated using the medians of quintiles/categories as continuous variables in the Cox models. In additional models, coffee and tea were mutually adjusted for.

In analyses by type of coffee, only data from 163,672 participants (Germany, Netherlands and United Kingdom), for whom the sum of caffeinated and decaffeinated coffee equals the total amount of coffee intake, were included. Due to the large number of non-consumers of decaffeinated coffee (35%) we considered 3 categories for this beverage: (i) C1: non-consumers, (ii) C2: consumers below the median (among consumers), and (iii) C3: consumers at/above the median (among consumers). To preserve comparability here, caffeinated coffee and tea were also analysed in 3 categories defined as for decaffeinated coffee.

In all analyses, potential confounders were: sex, self-reported diabetes (categorically: no, yes, unknown), education (categorically: no formal/primary school, technical/secondary school, university /longer, unknown), physical activity (categorically: inactive/moderately inactive, moderately active/active, unknown), smoking (categorically: never, former smoker, current smoker, unknown), ethanol intake (categorically: low: men< 10g/day, women <5 g/day; moderate: men 10-<40 g/day, women 5-<20 g/day; high: men ≥40 g/day, women ≥20 g/day), body mass index (categorically: ≤25 kg/m^2, >25 to <30 kg/m^2 , ≥30 kg/m^2) and energy intake (ordered, in sex-specific quintiles). In order to minimize residual confounding by smoking/ethanol intake, we further used more detailed variables (but with more missing values), accounting for intensity and/or duration of smoking and lifetime alcohol drinking. Deviations from log linearity of the associations between coffee/tea intakes and HCC risk were assessed by: a) comparing models including coffee/tea intakes as ordered, with models including both dietary exposures as categorical, using the Likelihood Ratio test (LRtest), b) by applying restricted cubic splines Cox regression models for coffee/tea intakes and testing (using the Wald test and the

LRtest) whether these models were of better fit as compared to models which assumed simpler, log linear associations between coffee/tea and HCC risk, and c) by inspecting the Akaike's Information Criterion (AIC) in models assuming restricted cubic splines for the indicated associations as compared to models of linear trends which are shown in Table 3.

We performed several sensitivity analyses (see Results). Furthermore, we investigated whether the estimated associations differed across strata defined by sex (men/women), diabetes (yes/no), smoking (never/former/current), ethanol intake (low/moderate/high as indicated above) and body mass index ($\leq$25 kg/m^2/ >25 to <30 kg/m^2 / $\geq$30 kg/m^2), by introducing interaction terms between quintiles/categories of coffee/tea intake (ordered) and each of the indicated variables (categorically). In order to evaluate whether the associations between coffee/tea intake and HCC risk varied by positivity status regarding hepatitis B virus (HBV) and/or hepatitis C virus (HCV), we used data from the nested case-control study[13] and introduced interaction terms in conditional logistic regression models between HBV/HCV status (yes/no) and coffee/tea intakes; in this analysis, coffee/tea intakes were considered in tertiles (T1-T3, using control-defined cut-off values) due to the small number of controls.

P<0.05 was considered statistically significant. All analyses were performed using STATA (Stata Corporation: Stata statistical software, release 11. College Station. TX: Stata Corporation; 2009).

RESULTS

After a median follow-up of 11 years, 1,622,408 and 3,744,060 person-years were accrued from the 145,039 (30%) men and 341,760 (70%) women of the study population, respectively, and 133 men and 68 women were diagnosed with HCC.

Table 1 presents the distribution of participants according to sex-specific quintiles of coffee intake, country and baseline characteristics. Overall median coffee consumption was 354 ml/d among men and 290 ml/d among women; 7% of the participants did not consume coffee. Coffee intake varied across countries, with the Danes consuming the highest quantities. Participants with higher coffee intakes were slightly older, more educated, reported less frequently diagnosis with diabetes, were more frequently smokers, consumed higher amounts of ethanol, had lower body mass index, were more active and had higher energy intake.

In Table 2, corresponding distributions as in Table 1 are presented by categories of tea intake. Among tea consumers (66% of the total cohort), median intakes were 107 ml/d for men and 190 ml/d for women. Distribution of participants across categories of tea intake varied across countries, with the highest intakes consumed in the UK. Consumers of high tea intakes were more educated, more active, former smokers, moderate ethanol drinkers, reported less frequently diabetes, and had lower body mass index.

Table 3 shows hazard ratios (HRs) for HCC incidence by quintiles/categories of coffee/tea intakes, separately (models 1 and 2) and after mutual adjustment (model 3).

Increased coffee intake was associated with a substantial, monotonic and statistically significant reduction in HCC risk, in all models. This inverse association was more pronounced when coffee and tea were considered simultaneously (HR_{Q5vsQ1}, 0.28; 95% confidence interval (CI), 0.16 to 0.50). Tea intake was also inversely associated with HCC incidence, with a linear trend apparent in all models (particularly model 3).

There was no statistical evidence indicating that models assuming a log linear association between coffee/tea intakes and HCC risk were of inferior fit as compared to models with no assumption for the type of association of coffee/tea with HCC risk (i.e., using coffee/tea intakes in quintiles/categories, categorically): $LRtest_{coffee}$ =0.707, $LRtest_{tea}$ =0.683. Similarly, there was no evidence that restricted cubic splines regression models were of better fit as compared to simpler models assuming log linear associations between coffee/tea and HCC risk (p-value from Wald test: coffee: 0.13; tea: 0.78). The AIC for model 3 of Table 3 of linear trends (AIC=2372.795) indicated a slightly better model fit as compared to the restricted cubic splines models for coffee (AIC=2379.004) and tea (AIC= 2409.564).

More detailed control for smoking (i.e., smoking intensity/duration) and alcohol intake (e.g. lifetime alcohol consumption), as well as, the inclusion of body mass index and energy intake as continuous rather than as categorical variables, generated very similar results.

Sensitivity analyses

Sensitivity analyses focussed on model 3 (Table 3). When subjects without missing values were studied (187 HCC cases/413,666 participants), HRs and 95% CIs were

essentially identical to those reported in Table 3. When 9,596 subjects (10 HCC cases) in the top/bottom 1% of the energy intake distribution were excluded, results were also similar to those previously reported (coffee: HR_{Q5vsQ1}, 0.26; 95% CI, 0.14 to 0.48 (*P*-trend <0.001); tea: HR_{C5vsC1}, 0.36; 95% CI, 0.18 to 0.73 (*P*-trend=0.002)). When analyses were restricted to the 167 histologically confirmed HCC cases with tea consumption information, the inverse associations of coffee/tea with HCC risk followed the same linear trends (coffee: *P*-trend <0.001; tea *P*-trend=0.009). Excluding the first 2 years of follow-up (171 HCC cases/442,961 participants analysed) did not alter the strength/pattern of the estimated associations (coffee: *P*-trend <0.001; tea: *P*-trend=0.002). Finally, using sex-and-country specific quintiles/categories for coffee and tea, resulted in somewhat less striking, albeit still statistically significant associations for coffee (HR_{Q2vsQ1}, 0.57; 95% CI, 0.39 to 0.85; HR_{Q3vsQ1}, 0.57; 95% CI, 0.36 to 0.89; HR_{Q4vsQ1}, 0.56; 95% CI, 0.36 to 0.87; HR_{Q5vsQ1}, 0.45; 95% CI, 0.28 to 0.74; *P*-trend=0.002). For tea, the apparent linear trend was no longer statistically significant, possibly on account of scarcity of data (*P*-trend=0.08).

Examination of effect-modifications

Interactions were evaluated among participants without missing data and were, generally, far from statistically significant. The associations of both beverages were considerably weaker among diabetics, but the interaction terms were statistically non-significant (coffee, *P*-interaction=0.14; tea, *P*-interaction =0.20). There was a suggestion for tea-by-sex interaction (*P*-interaction=0.06), possibly on account of the small number of female HCC cases; HRs (95% CIs) per category increase in tea

consumption were 0.80 (0.68 to 0.94) among men, but 1.08 (0.84 to 1.38) among women.

In the nested case-control analysis, odds ratios (OR) for HCC risk, adjusted for HBV/HCV status, smoking, ethanol intake, education, and mutually for coffee and tea intakes were: coffee: OR_{T3vsT1}, 0.54 (95% CI, 0.19 to 1.58), *P*-trend=0.25; tea: OR_{T3vsT1}, 0.36 (95% CI, 0.13 to 0.99), *P*-trend 0.04. No evidence for effect modification of the impact of coffee/tea intakes on HCC risk according to HBV/HCV status was observed (coffee: *P*-interaction=0.78; tea: *P*-interaction=0.50).

Caffeinated and decaffeinated coffee

In analyses of 163,672 participants (64 HCC cases) from Germany, Netherlands and UK, the inverse association of coffee with HCC risk was seen across the three categories of caffeinated (*P*-trend=0.009), but not of decaffeinated coffee (*P*-trend=0.45). Compared to caffeinated coffee, the inverse association of decaffeinated coffee with HCC risk was considerably weaker and statistically non-significant ($HR_{C2vs.C1}$: 0.94, 95% CI, 0.39 to 2.28; $HR_{C3vs.C1}$:0.74, 95% CI, 0.36 to 1.51).

DISCUSSION

In a multi-centre European cohort, we found evidence that intakes of coffee and, to a lesser extent, tea are associated with lower HCC incidence. Both associations followed statistically significant linear trends, which were also generally apparent in

subgroup analyses. Compared to those with minimal or no consumption of coffee, and adjusted also for tea intake, those in the highest quintile of coffee intake had a statistically significantly lower HCC risk by about 70%. For tea, the corresponding contrast was milder than that for coffee, with the risk in the highest quintile being about 60% lower in comparison to the lowest quintile (composed exclusively by non-consumers). This is the first multi-centre cohort study in a western population which has investigated simultaneously and with mutual adjustment the association of coffee and tea intakes with HCC risk.

Our results are in line with those reported in previous case-control[14-16] and cohort[17-22] Asian studies, as well as in three case-control studies[23-25] and in two, moderately-sized, cohort studies conducted in Europe[5,6] with respect to: a) the inverse association of coffee consumption with HCC risk, b) the linear trend in risk reduction with increasing coffee intake, and c) the consistency of these findings across various subgroups. In a recent meta-analysis,[8] including all indicated studies, as well as three studies reporting statistically non-significant inverse[19,26] or null[27] associations, the summary relative risk for HCC for any vs. no coffee consumption was 0.60 (95% CI, 0.50 - 0.71), with a dose-response trend. With the exception of one Italian case-control study, [25] studies on tea consumption and HCC risk have been conducted exclusively in Asia (where green tea consumption is more frequent than in Europe); the results are collectively inconclusive. Two studies reported statistically significant inverse associations,[28,29] four inverse but statistically non-significant associations,[30-33] two null associations,[19,34] whereas three reported positive, albeit statistically non-significant associations.[17, 25, 35] A meta-analysis of these studies[9] pointed to a suggestive inverse association of tea with primary liver cancer. Our study, the first

cohort study outside Asia, indicates an inverse, dose-dependent association of tea with HCC risk, which is not incompatible with the results of the indicated meta-analysis, although our findings point to a stronger inverse association.

Several mechanisms could underlie the inverse association between coffee intake and HCC. Coffee has been inversely related to chronic liver disease, [36,37] cirrhosis,[37,38] or diabetes mellitus.[39] In previous studies, however, the inverse association between coffee and HCC risk was evident in subjects irrespectively of chronic liver disease, or HBV/HCV status.[8] When we excluded the first 2 years of follow-up, which would exclude a fraction of cases with underlying liver disease, results were largely unchanged. Moreover, adjusting for chronic HBV/HCV infection in our nested case-control study, did not materially affect the results, nor was there a statistically significant interaction between virus carrier state and coffee (and tea) intake with respect to HCC risk – a finding with considerable clinical importance,[40] given the high HCC risk of HBV/HCV carriers. Of note, our results were adjusted for diabetes and there was no evidence for diabetes-by-coffee (or tea) interaction.

Coffee contains several hundred chemical compounds including caffeine, diterpenes, chlorogenic acids and flavonoids, with reported anti-hepatocarginogenic effects.[41] Regarding caffeine intake, in a subset of our data, intake of caffeinated coffee, tea and decaffeinated coffee appear to be inversely related to HCC risk but the association is strong and statistically significant for caffeinated coffee, weaker and statistically non-significant for tea and still weaker for decaffeinated coffee. Taking into account, the correspondence with the caffeine content of the three beverages and given that caffeine content (not content of other antioxidant compounds)[42] is the defining

difference between caffeinated and decaffeinated coffee, a key role of caffeine cannot be excluded. We did not have available information on the amount of caffeine intake (from all food/beverage sources) in order to better explore the potential role of caffeine on the inverse association of coffee with HCC risk. The possible differential association of caffeinated and decaffeinated coffee with HCC risk needs to be further explored, preferably in other large cohort studies.

Regarding tea, experimental studies have suggested a hepatoprotective effect, mainly invoking antioxidative properties of green tea polyphenols.[43] There was no adequate information on type of tea in our cohort, but Europeans are likely to consume mostly black rather than green tea. Given the inconclusive collective evidence in the literature, further studies are needed to affirm any protective role of tea on HCC risk before exploring the underlying mechanisms.

Strengths of our study are its cohort design, its multi-centre coverage allowing to examine a variable range of tea and coffee intakes across European countries, the use of validated questionnaires, the relatively long follow-up, the common identification criteria of incident HCC and the available information about potential confounders. A limitation of our study is the unavoidable modest number of HCC outcomes, given the low incidence of the disease in most European countries. Another limitation stems from the lack of data about brewing methods across countries, as well as from complications arising from the different volume/concentration of coffee consumption across countries. Errors in reporting beverage consumption cannot be ruled out, but this is more likely to result in random misclassification of intakes, thus generating underestimation of true associations. Bias in the estimated associations could have

been introduced if cases had modified their coffee/tea consumption during the prediagnostic period of their disease, but excluding cases diagnosed in the first 2-years of follow-up generated essentially identical results.

In conclusion, in a large prospective study across European countries, we found evidence that increased coffee and tea intakes are associated, in a dose-dependent pattern, with lower HCC risk. The estimated risk reduction was stronger for coffee than for tea, whereas there was no convincing evidence for an association of decaffeinated coffee with HCC. Given the apparent lack of heterogeneity of the HCC associations with coffee and tea by HBV/HCV positivity status or other risk factors, the results may even have important implications for high HCC risk subjects. Mechanistic studies could clarify whether the noted associations could be attributed to caffeine, or, to other constituents of these beverages.

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Conflict of interest

The authors declared no conflict of interest.

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Table 1. Distribution of study participants by quintiles[a] of coffee intake, as well as, by country of origin and baseline characteristics. The European Prospective Investigation into Cancer and nutrition study.

	Quintiles of coffee intake (ml/day)				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Median (range): males	***17.3 (0 to 83.3)***	***140.5 (83.3 to 200.4)***	***375 (200.5 to 476.9)***	***556.4 (477.2 to 830.4)***	***1000 (831.3 to 4500)***
Median (range): females	***3.8 (0 to 60)***	***125.9 (60 to 191.9)***	***290.4 (191.9 to 375)***	***500 (375 to 580.2)***	***856.9 (580.3 to 6250)***
Country[b] (%)					
France	22.1	21.9	27.0	16.9	12.0
Italy	35.6	56.7	7.4	0.3	0.04
Spain	44.7	34.0	17.8	2.8	0.7
UK	26.7	20.5	10.9	21.7	20.1
Netherlands	8.2	5.0	21.8	29.0	36.0
Greece	22.3	43.8	26.1	6.3	1.5
Germany	11.9	11.2	32.4	27.9	16.7
Sweden	7.7	10.5	27.7	32.4	21.7
Denmark	7.4	6.6	3.1	27.0	55.9
Norway	14.4	7.2	30.8	25.9	21.7
Age (years): Mean (SD)	50 (11)	52 (10)	51 (9)	51 (10)	52 (9)
Sex[b] (%)					
males	20.4	19.6	21.5	18.5	20.0
females	20.1	21.2	18.7	20.4	19.6
Self-reported diabetes mellitus[b] (%)					
No	20.2	21.0	19.6	19.7	19.5

Yes	24.7	24.9	19.3	15.6	15.5
Unknown	16.2	12.0	18.3	25.5	28.0
Educational level[b] (%)					
None / Primary	23.2	26.9	17.9	14.6	17.4
Technical/professional/secondary	17.6	17.3	20.4	22.5	22.3
University degree/longer	20.1	18.9	21.3	21.4	18.4
Not specified	26.7	22.5	12.4	21.2	17.3
Smoking[b] (%)					
Never	24.8	23.0	19.6	19.0	13.6
Former	18.0	19.0	20.5	21.6	21.0
Current	12.6	18.0	17.9	19.5	32.0
Unknown	20.7	19.9	25.8	19.2	14.3
Ethanol Intake (g/day) [b] (%)					
low [c]	23.5	21.2	19.9	18.6	16.8
moderate [c]	16.3	19.8	19.3	21.8	22.8
high [c]	17.1	21.6	18.8	19.4	23.2
Body Mass Index[b] (kg/m^2) (%)					
<=25	20.1	19.4	20.0	21.0	19.5
>25 - <30	19.2	21.3	19.5	19.3	20.6
>=30	22.8	24.5	18.0	16.3	18.4
Physical Activity Index[b] (%)					
moderately inactive [d]	22.5	24.6	18.8	17.6	16.5
moderately active [d]	18.4	18.6	18.5	21.3	23.2
unknown	14.2	7.5	28.7	26.3	23.3
Energy Intake (kcal/day) : mean (SD)	2051.4 (686.0)	2109.6 (677.0)	2062.7 (661.1)	2069.8 (662.9)	2130.2 (702.3)

Total (Number)	98,148	100,953	95,231	96,413	96,054

[a] Sex-specific quintiles in the overall cohort

[b] Numbers in cells do not always add up to 100% horizontally due to rounding

[c] Ethanol Intake: Low: Males:<10 g/day / Females:<5 g/day; Moderate: Males:10g/day to <40g/day / Females:5g/day to 20g/day; High: Males:>40 g/day; Females:>20 g/day.

[d] Based on occupational physical activity and physical activity during cycling and sports

Table 2. Distribution of study participants by categories[a] of tea intake, as well as, by country of origin and baseline characteristics. The European Prospective Investigation into Cancer and nutrition study.

	Categories of tea intake (ml/day)				
	C1	**C2**	**C3**	**C4**	**C5**
Median (range): males	***0***	***3.3 (0.3 to 16.4)***	***37 (16.4 to 106.8)***	***250 (107.1 to 475)***	***855 (480 to 2375)***
Median (range): females	***0***	***8.2 (0.0006 to 28.6)***	***87.9 (28.6 to 190)***	***360 (190.4 to 475)***	***855 (475.1 to 5937.5)***
Country[b] (%)					
France	41.0	10.2	16.9	19.0	13.0
Italy	45.1	23.8	24.8	5.9	0.4
Spain	96.0	0.5	1.9	1.5	0.1
UK	2.8	14.3	11.0	34.4	37.6
Netherlands	10.5	8.0	23.1	44.3	14.2
Greece	46.2	44.5	8.0	1.2	0.1
Germany	24.1	6.0	35.4	26.3	8.2
Sweden	52.4	16.6	13.3	12.6	5.1
Denmark	16.1	19.3	20.8	10.0	33.8
Norway	NA	NA	NA	NA	NA
Age a(years): Mean (SD)	53 (9)	50 (11)	50 (10)	51 (11)	53 (11)
Sex[b] (%)					
males	35.3	17.4	15.2	18.2	14.0
females	33.3	16.7	16.8	17.5	15.7
Self reported diabetes mellitus[b] (%)					
No	33.6	17.1	16.5	17.9	15.0

Yes	47.5	15.4	13.7	12.9	10.5
Unknown	31.2	13.9	12.6	17.5	24.9
Educational level[b] (%)					
None / Primary	53.1	16.5	13.4	8.8	8.1
Technical/professional/secondary	27.7	17.6	18.1	20.3	16.4
University degree/longer	24.1	17.0	17.7	22.6	18.7
Not specified	11.2	12.9	11.2	30.2	34.5
Smoking[b] (%)					
Never	33.3	16.6	16.4	18.5	15.2
Former	29.8	15.7	16.5	20.1	17.8
Current	40.8	19.2	15.8	12.9	11.3
Unknown	29.9	16.8	15.1	20.0	18.2
Ethanol Intake (g/day)[b] (%)					
low [c]	35.1	17.8	15.5	17.3	14.3
moderate [c]	30.8	16.3	17.2	19.0	16.7
high [c]	37.8	15.5	16.8	16.0	13.9
Body Mass Index (kg/m^2) [b] (%)					
<=25	28.1	16.7	17.1	20.5	17.6
>25 - <30	37.5	17.1	15.8	16.0	13.6
>=30	46.2	17.5	14.5	11.9	10.0
Physical Activity Index [b] (%)					
moderately inactive[d]	38.6	17.1	15.1	15.6	13.7
moderately active[d]	28.6	17.1	17.8	19.8	16.8
unknown	12.9	9.3	19.8	38.3	19.7
Energy Intake (kcal/day) : mean (SD)	2154.6 (691.5)	2053.1 (682.8)	2140.3 (698.3)	2084.2 (651.5)	2132.3 (672.2)

Total [e] (Number)	153,097	76,393	73,424	79,872	68,135

[a] Categories of tea intake were defined as: non-consumers (C1); and the sex-specific quartiles among tea consumers (C2-C5) in the overall cohort.

[b] Numbers in cells do not always add up to 100% horizontally due to rounding

[c] Ethanol Intake: Low: Males:<10 g/day / Females:<5 g/day; Moderate: Males:10g/day to <40g/day / Females:5g/day to 20g/day; High: Males:>40 g/day; Females:>20 g/day.

[d] Based on occupational physical activity and physical activity during cycling and sports

[e] Norway is excluded due to lack of information about tea intake

Table 3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) of hepatocellular carcinoma (HCC) incidence according to quintiles[a] of coffee and categories[b] of tea intake in the European Prospective Investigation into Cancer and nutrition cohort.

	HCC cases/N	Model 1[c]		Model 2[d]		Model 3[e]	
		HR	95% CI	HR	95% CI	HR	95% CI
Coffee Intake (quintiles)							
Q1	47 / 98,148	1		1		1	
Q2	49 / 100,953	0.96	(0.63 to 1.44)	0.91	(0.60 to 1.38)	0.85	(0.56 to 1.29)
Q3	38 / 95,231	0.75	(0.46 to 1.19)	0.71	(0.44 to 1.14)	0.63	(0.39 to 1.02)
Q4	36 / 96,413	0.67	(0.41 to 1.10)	0.61	(0.37 to 1.01)	0.49	(0.29 to 0.82)
Q5	31 / 96,054	0.48	(0.28 to 0.82)	0.38	(0.22 to 0.66)	0.28	(0.16 to 0.50)
P- trend		*0.004*		*<0.001*		*<0.001*	
Tea Intake (categories)							
C1	85 / 153,097	1		1		1	
C2	37 / 76,393	0.96	(0.62 to 1.49)	1.04	(0.67 to 1.61)	1.05	(0.68 to 1.63)
C3	35 / 73,424	0.90	(0.58 to 1.41)	1.01	(0.65 to 1.58)	0.98	(0.63 to 1.53)
C4	24/ 79,872	0.68	(0.40 to 1.16)	0.82	(0.48 to 1.41)	0.71	(0.41 to 1.23)
C5	18 / 68,135	0.49	(0.27 to 0.89)	0.60	(0.32 to 1.10)	0.41	(0.22 to 0.78)
P-trend		*0.01*		*0.06*		*0.003*	

Abbreviations: HR, Hazard ratio; CI, Confidence Interval; HCC, Hepatocellular carcinoma

[a] Sex-specific quintiles (Q1-Q5) in the overall cohort

[b]Categories of tea intake were defined as: non-consumers (C1); and the sex-specific quartiles among tea consumers (C2-C5) in the overall cohort.

[c]Stratified for age at recruitment (in 1-year intervals) and for centre. Adjusted for sex. Norway was not included in analyses concerning tea intake as this information was not available.

[d]Stratified for age at recruitment (in 1-year intervals) and for centre. Adjusted for sex, diabetes mellitus (self reported at enrolment), education, body mass index, smoking, physical activity, alcohol intake, categorically as in Table 2 and energy intake (ordered in quintiles). Norway was not included in analyses concerning tea intake as this information was not available.

[e]As model 2 but simultaneously including tea and coffee intake. Norway was not included in analyses concerning tea intake as this information was not available.