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Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort

Mia Hashibe*[,1,2], Carlotta Galeone[3], Saundra S Buys[4], Lisa Gren[1], Paolo Boffetta[5], Zuo-Feng Zhang[6] and Carlo La Vecchia[7]

[1]Division of Public Health, Department of Family and Preventive Medicine, University of Utah School of Medicine, 375 Chipeta Way, Suite A, Salt Lake City, UT 84108, USA; [2]Huntsman Cancer Institute, University of Utah School of Medicine, 2000 Circle of Hope, Salt Lake City, UT 84108, USA; [3]Division of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Via Bicocca degli Arcimboldi 8, Milan 20126, Italy; [4]Department of Internal Medicine and Huntsman Cancer Institute, University of Utah School of Medicine, 2000 Circle of Hope, Salt Lake City, UT 84108, USA; [5]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Room 3-55 1425 Madison Avenue, New York, NY 10029, USA; [6]Department of Epidemiology, UCLA Fielding School of Public Health, 71-225 CHS, Box 951772, Los Angeles, CA 90095, USA and [7]Department of Clinical Sciences and Community Health, University of Milan, Via Vanzetti, 5, Milan 20133, Italy

Background: The association between coffee intake, tea intake and cancer has been extensively studied, but associations are not established for many cancers. Previous studies are not consistent on whether caffeine may be the source of possible associations between coffee and cancer risk.

Methods: In the Prostate, Lung, Colorectal, and Ovarian cancer screening trial, of the 97 334 eligible individuals, 10 399 developed cancer. Cancers included were 145 head and neck, 99 oesophageal, 136 stomach, 1137 lung, 1703 breast, 257 endometrial, 162 ovarian, 3037 prostate, 318 kidney, 398 bladder, 103 gliomas, and 106 thyroid.

Results: Mean coffee intake was higher in lower education groups, among current smokers, among heavier and longer duration smokers, and among heavier alcohol drinkers. Coffee intake was not associated with the risk of all cancers combined (RR = 1.00, 95% confidence interval (CI) = 0.96–1.05), whereas tea drinking was associated with a decreased risk of cancer overall (RR = 0.95, 95% CI = 0.94–0.96 for 1+ cups per day *vs* <1 cup per day). For endometrial cancer, a decreased risk was observed for coffee intake (RR = 0.69, 95% CI = 0,52–0.91 for ⩾2 cups per day). Caffeine intake was not associated with cancer risk in a dose–response manner.

Conclusions: We observed a decreased risk of endometrial cancer for coffee intake, and a decreased risk of cancer overall with tea intake.

The association between coffee intake and various cancers has been extensively studied, but associations are not established for many cancers. Coffee intake may not be associated with the risk of overall cancer (RR = 1.03, 95% confidence interval (CI) = 0.97–1.10), according to a meta-analysis of prospective studies (Malerba *et al*, 2013b). However, recent studies have been suggestive of a protective effect of coffee against head and neck cancer, oesophageal squamous cell carcinoma, and endometrial cancer, with dose–response relations (La Vecchia and Tavani, 2007; Bravi *et al*, 2009a, b; Galeone *et al*, 2010; Turati *et al*, 2011). There have been multiple recent meta-analyses showing a reduced risk of prostate cancer risk with greater coffee intake (Cao *et al*, 2014; Discacciati *et al*, 2014; Huang *et al*, 2014; Lu *et al*, 2014; Zhong *et al*, 2014). The protective effects observed tended to be for very high coffee intake (more than 4–7 cups of coffee per day). On the other hand, some cancers are thought to have no association

*Correspondence: Professor M Hashibe; E-mail: mia.hashibe@utah.edu

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with coffee intake (oesophageal adenocarcinoma, stomach, lung, ovarian, and thyroid cancer and glioma).

Tea intake may also be protective against some cancers, although again data are inconsistent. Green tea may be protective against breast cancer and black tea may increase risk according to a meta-analysis of five cohort studies and eight case–control studies (Sun *et al*, 2006). A meta-analysis of tea intake including seven case–control and five cohort studies was suggestive of a protective effect (RR = 0.85, 95% CI = 0.71–1.01) against ovarian cancer (Steevens *et al*, 2007), although a more recent meta-analysis suggested no association with ovarian cancer (Braem *et al*, 2012). Similarly, a decreased kidney cancer risk due to tea intake was also suggested in a pooled analysis of 13 prospective studies (RR = 0.85, 95% CI = 0.71, 1.02; Lee *et al*, 2007). No consistent associations were observed between tea intake and head and neck cancer (Galeone *et al*, 2010), bladder cancer (Wu *et al*, 2013; Bai *et al*, 2014), or thyroid cancer (Mack *et al*, 2003).

Some studies have reported an association with cancer for caffeinated coffee but not for decaffeinated coffee. Few studies were able to examine total caffeine intake from all dietary sources. A large proportion of studies that have assessed the association between total caffeine intake and cancer have been null (Najem *et al*, 1982; Folsom *et al*, 1993; Slattery and West, 1993; Michels *et al*, 2002; Hirose *et al*, 2007; Ishitani *et al*, 2008; Song *et al*, 2008; Boggs *et al*, 2010). Studies reporting an association between caffeine intake and cancer include an inverse association with ovarian cancer (Jordan *et al*, 2004; Tworoger *et al*, 2008), as well as an increased risk for ovarian cancer (Kuper *et al*, 2000). As caffeine is a component of coffee that can induce biological effects and may induce apoptosis (Bohn *et al*, 2014), it is of interest to assess whether caffeine is associated with cancer risk.

Considering that coffee and tea consumption are a highly prevalent lifestyle factor in the world, it is of interest to clarify the role of coffee and tea in cancer overall and in specific cancer sites. We investigated the relation between coffee and tea consumption and cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) prospective study.

MATERIALS AND METHODS

The PLCO trial is a large-scale clinical trial aimed at determining whether select cancer screening tests reduce deaths from prostate, lung, colorectal, and ovarian cancer. The trial started in 1992 and ended enrollment in 2001. Approximately 155 000 women and men between the ages of 55 and 74 were recruited into the PLCO trial at 10 centres across the United States (Alabama, Michigan, Colorado, Hawaii, Wisconsin, Minnesota, Pennsylvania, Utah, Missouri, and Washington DC). At entry, participants were randomised to one of two study groups. One group received routine health care from their health providers. The other received a series of exams to screen for prostate, lung, colorectal, and ovarian cancers. Screening of participants ended in late 2006. Follow-up will continue for up to 10 more years to determine the benefits or harms of screening. Written informed consent was obtained from all study participants. Ethical approval for human subjects' research was obtained at each of the centres.

The data used for this study include the follow-up information up to May 2011. Subjects randomised to either study arm (intervention or control) were eligible if they had completed the baseline questionnaire and the diet history questionnaire, which was administered to participants in both groups starting in 1998. The dietary history questionnaire has been validated in three different studies (Subar *et al*, 2001; Thompson *et al*, 2002; Millen *et al*, 2009). Of the 154 900 study participants recruited into the PLCO study, 111 513 participants completed both the baseline questionnaire and the diet history questionnaire. Of the 111 513 participants with valid questionnaires, participants were excluded because: (a) they had cancer before entry into the PLCO study ($n = 9673$) or (b) they did not have follow-up time ($n = 4506$). Thus, the remaining cohort consisted of 97 334 individuals, of which 10 399 developed any malignant cancer. We excluded from the present analysis cancers of the pancreas, liver, and colorectum, which will be or have been the object of in depth analysis by other investigators (Dominianni *et al*, 2013). We focused on cancers where recent published studies suggested associations with coffee. There were cases of: 145 head and neck cancers, 99 esophageal cancers, 136 stomach cancers, 1137 lung cancers, 1703 breast cancers, 257 endometrial cancers, 162 ovarian cancers, 3037 prostate cancers, 318 kidney cancers, 398 bladder cancers, 103 gliomas, and 106 thyroid cancers. The total number of patients with the cancers of interest was 7601. Cancer cases were diagnosed from enrollment completion in 2001 to May 2011. An annual study update was used to ascertain cancer diagnoses, and was mailed annually to the study participants. Participants were asked if they were diagnosed with cancer, the type of cancer, date of diagnosis, hospital or clinic of diagnosis, and physician contact information. For every cancer reported, medical record abstraction included the cancer diagnosis date and ICD-O-2 code. Death status was obtained by the administration of the Annual Study Update questionnaire, reports from relatives, friends, or physicians, and National Death Index plus searches. Study centres attempted to obtain a death certificate for each death that occurred on or before 31 December 2009.

If the study participant was diagnosed with cancer after study entry, which ranged from 1992 to 2001, and before completion of the dietary questionnaire, they were not eligible. The entry date is taken as the maximum of randomisation date, baseline questionnaire completion date, and dietary history questionnaire completion date. In this analysis, dietary history questionnaire completion is necessary for the coffee and tea information, thus the entry date becomes the dietary history questionnaire completion date.

Although the screening arm was screened for prostate, lung, colorectal, and ovarian cancers, they did not necessarily have higher incidence rates of cancer. Of the 10 399 cancer cases, 5243 were in the control arm and 5156 were in the intervention arm. For the specific cancers, the numbers for control *vs* intervention arm were: 68 *vs* 77 in head and neck cancers, 53 *vs* 46 in esophageal cancers, 61 *vs* 75 in stomach cancers, 560 *vs* 577 in lung cancers, 870 *vs* 833 in breast cancers, 143 *vs* 111 in endometrial cancers, 77 *vs* 85 in ovarian cancers, 1521 *vs* 1485 in prostate cancers, 140 *vs* 178 in kidney cancers, 213 vs 184 in bladder cancers, 56 *vs* 47 in gliomas, and 59 *vs* 47 in thyroid cancers. According to a χ^2 test, the number of cancer cases by study arm was not statistically significantly different, except for breast cancer (1.85% of control group were diagnosed with breast cancer, 1.70% of intervention group were diagnosed with breast cancer; *P*-value for $\chi^2 = 0.0411$), and endometrial cancer (0.3% of control group and 0.23% of intervention group were diagnosed; *P*-value for $\chi^2 = 0.0182$).

The baseline questionnaire included information on age, sex, race, education, marital status, cigarette smoking (frequency, years), family history of cancer, weight (at age 20 years, age 50 years and current), and height. The diet history questionnaire administered beginning in 1998, included information on numerous food items including coffee, tea, and caffeine intake. The questions on coffee were 'Over the past 12 months, how many cups of coffee, caffeinated, or decaffeinated did you drink?', 'How often was the coffee you drank decaffeinated?'. The size of the cup was not indicated. The answer options for the cups of coffee were none, <1 cup per month, 1–3 cups per month, 1 cup per week, 2–4 cups per week, 5–6 cups per week, 1 cup per day, 2–3 cups per day, 4–5 cups per day, and 6 or more cups per day. The questions on tea were 'How many glasses of ICED tea, caffeinated, or decaffeinated did you drink?', 'How often was the iced tea you drank

decaffeinated or herbal tea?', 'How many cups of HOT tea, caffeinated, or decaffeinated did you drink?', 'How often was the hot tea you drank decaffeinated or herbal tea?'. The questions on iced and hot tea were summed to obtain the total tea intake. The answer options for the cups of tea were the same as for coffee, as specified above. There were also questions on whether sugar, honey, artificial sweeteners, non-dairy creamer, cream or half and half, and/or milk were added to the coffee or tea.

Nutrient databases were developed for the dietary questionnaire based on the NDS-R sample data by the PLCO research team. The nutrient values (including caffeine) were calculated from the database for each subject based on the frequency with which they said they ate/drank each food or beverage and also the portion size. For example, if a subject said they drank a coffee three times per week then the nutrient values for a coffee were multiplied by the frequency of three times per week and then converted to a daily

Table 1. Characteristics of the PLCO cohort and cancer cases

	Cohort				Any cancer			
	n	%	Mean coffee intake (cups per day)	mean Tea intake (cups per day)	*n*	%	Mean coffee intake (cups per day)	Mean tea intake (cups per day)
Total	97 334		1.9	0.65	10 399		2.0	0.63
Age at enrollment (years)								
55–59	17 711	18.2	1.9	0.71	1440	13.8	2.1	0.69
60–64	27 870	28.6	1.9	0.66	2800	26.9	2.1	0.62
65–69	26 261	27.0	1.9	0.64	3031	29.1	2.0	0.62
> =70	25 492	26.2	1.8	0.62	3128	30.1	1.9	0.61
Sex								
Male	46 771	48.1	2.1	0.56	6209	59.7	2.2	0.55
Female	50 563	51.9	1.7	0.74	4190	40.3	1.8	0.74
Race								
White, non-Hispanic	88 515	90.9	2.0	0.65	9554	91.9	2.1	0.63
Other	8819	9.1	1.2	0.65	845	8.1	1.3	0.65
Education								
⩽11 years	5773	5.9	2.1	0.55	671	6.5	2.2	0.51
12 years or completed high school	22 656	23.3	2.0	0.61	2316	22.3	2.1	0.58
Post high school training	33 501	34.4	1.9	0.66	3557	34.2	2.0	0.63
College graduate or postgraduate	35 216	36.2	1.8	0.69	3855	37.1	1.9	0.68
Missing	188	0.2						
Tobacco smoking status								
Never smoker	46 751	48.0	1.5	0.68	4367	42.0	1.5	0.65
Current smoker	8820	9.1	3.0	0.61	1357	13.0	3.1	0.60
Former smoker	41 743	42.9	2.1	0.63	4675	45.0	2.2	0.62
missing	20	0.0						
Tobacco smoking frequency (cigarettes per day)								
Never smoker	46 751	48.0	1.5	0.68	4367	42.0	1.5	0.65
1–10	13 062	13.4	1.9	0.67	1254	12.1	1.9	0.62
11–20	18 702	19.2	2.3	0.61	2228	21.4	2.3	0.61
21–30	10 088	10.4	2.5	0.60	1334	12.8	2.6	0.62
>30	8615	8.9	2.6	0.63	1216	11.7	2.7	0.62
Missing	116	0.1						
Tobacco smoking duration (years)								
Never smoker	46 751	48.0	1.5	0.68	4367	42.0	1.5	0.65
1–10	7604	7.8	1.9	0.69	731	7.0	1.9	0.65
11–20	10 585	10.9	2.1	0.64	1166	11.2	2.1	0.60
>20	31 318	32.2	2.5	0.61	4135	39.8	2.6	0.61
Missing	1076	1.1						
Tobacco smoking, years since quitting for former smokers								
>0 to 2	2473	2.5	2.5	0.67	331	3.2	2.8	0.63
3–5	2520	2.6	2.3	0.60	345	3.3	2.3	0.55
6–10	5036	5.2	2.3	0.65	598	5.8	2.2	0.57
11–20	10 547	10.8	2.2	0.60	1182	11.4	2.3	0.61
>20	20 351	20.9	2.1	0.65	2219	21.3	2.0	0.63
Missing	836	0.9						
Alcohol drinking								
Never drinker	4081	4.2	1.2	0.60	380	3.7	1.4	0.55
<0.5 Drink per day	60 482	62.1	1.7	0.70	6214	59.8	1.9	0.70
0.5–0.9 Drink per day	9583	9.8	2.1	0.63	1029	9.9	2.2	0.59
1–1.49 Drinks per day	5500	5.7	2.3	0.60	619	6.0	2.4	0.51
1.5–1.9 Drinks per day	3823	3.9	2.3	0.58	414	4.0	2.3	0.53
2–2.4 Drinks per day	4480	4.6	2.3	0.57	501	4.8	2.3	0.60
⩾2 Drinks per day	9385	9.6	2.4	0.48	1242	11.9	2.4	0.44

Abbreviation: PLCO = Prostate, Lung, Colorectal, and Ovarian.

value. The nutrient totals were then summed over all foods to give the total daily nutrient intake for each subject. The largest contributors to caffeine intake were coffee, tea, and soda/soft drinks.

Statistical methods. We estimated hazard ratios and the corresponding 95% CIs with the Cox proportional hazards model. Follow-up time was calculated from the age at dietary questionnaire until the occurrence of one of the following events: diagnosis of cancer, death, or the end of follow-up. We adjusted on age (continuous), sex, race (white non-Hispanic *vs* others), education (categories as shown in Table 1), cigarette pack-years (continuous), and alcohol drinking frequency (mg of alcohol per day, continuous), where appropriate. All analyses were conducted with the SAS program version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

There were 97 334 individuals in the cohort, of which 10 399 were diagnosed with cancer. By age group, there did not appear to be any major differences in mean coffee consumption (Table 1). By sex, men drank more coffee per day than women, whereas women drank more tea than men. By race/ethnicity groups, White non-Hispanic individuals had a higher frequency of coffee drinking. Mean coffee intake was also higher in lower education groups, among current smokers, among heavier frequency smokers, among longer duration smokers, and among heavier drinkers. In contrast, mean tea consumption was higher in higher education groups, and never smokers. As expected, there were a higher proportion of heavier drinkers and heavier smokers in the cancer case group compared with the overall cohort.

Coffee intake was not associated with the risk of all cancers combined (Table 2). The number of cancer cases who drank coffee in the <1 cup per day groups were 1583 for all cancers, 17 for head and neck cancer, 16 for esophageal cancer, 9 for stomach cancer, 125 for lung cancer, 298 for breast cancer, 60 for endometrial cancer, 24 for ovarian cancer, 445 for prostate cancer, 46 for kidney cancer, 50 for bladder cancer, 17 for glioma, and 15 for thyroid cancer. For esophageal cancer, there appeared to be an increased risk for drinking 1–1.9 cups per day compared with <1 cup per day, although there was no overall dose–response trend. For lung cancer, an increased risk was observed for every one cup increase in coffee intake, but without a significant *P*-value for trend. A reduced risk of kidney cancer was suggested by the RR for every 1 cup per day increase in coffee intake, but again without a dose–response suggested for the categories of coffee drinking. For endometrial cancer, a decreased risk was observed, with a significant *P*-value for trend ($P = 0.009$), although the point estimates did not suggest a trend and instead suggested similar protective risk ratios for the two coffee drinking categories.

We conducted the analysis separately for regular coffee and decaffeinated coffee, but did not observe any strong associations or trends. We also estimated risk ratios for higher frequencies of coffee intake (4 or more cups/day) but did not observe any associations, except for kidney cancer (RR = 0.43, 95% CI = 0.20–0.93) where an overall dose–response was not observed (*P* for trend = 0.1015). For all cancers, the RRs were 0.99 (0.93–1.06) for drinking 2–3.9 cups per day and 1.00 (0.91–1.11) for drinking 4 or more cups per day.

Among the 46 751 never smokers in the cohort, 4367 developed cancer. Among these never smokers, associations of coffee intake with the risk of cancer overall or for any specific cancer were not detected. The overall cancer RRs for coffee drinking among never smokers were 1.03 (95% CI = 0.95–1.13) for 1–1.9 cups per day and 1.01 (95% CI = 0.95–1.08) for ⩾2 cups per day (*P* for trend = 0.6918). The endometrial cancer RRs for coffee drinking among never smokers were 0.67 (95% CI = 0.41–1.09) for 1–1.9 cups per day and 0.71 (95% CI = 0.50–1.01) for ⩾2 cups per day (*P* for trend = 0.0538).

For endometrial cancer, we further adjusted on BMI (<18.5 kg m^{-2}, 18.5–24.9 kg m^{-2}, 25–29.9 kg m^{-2}, 30+ kg m^{-2}),

Table 2. Coffee intake and cancer risk in the PLCO cohort

		Coffee intake (caffeinated and decaffeinated)								
			<1 Cup per day	1–1.9 Cups per day			⩾2 Cups per day			
	Total cases/cohort	Per cup	Cases/cohort	Cases/cohort	RR	95% CI	Cases/cohort	RR	95% CI	*P* for trend
All cancers[a]	10 399/96 024	1.00 (0.99–1.01)	3120/31 223	1580/14 749	1.01	0.95–1.08	5699/50 052	1.00	0.96–1.05	0.9932
Head and neck[a]	145/96 024	0.99 (0.91–1.09)	31/31 223	18/14 749	1.08	0.60–1.94	96/50 052	1.04	0.68–1.58	0.9047
Oesophageal[a]	99/96 024	1.03 (0.92–1.15)	22/31 223	23/14 749	1.9	1.06–3.43	54/50 052	0.93	0.56–1.56	0.4746
Stomach[b]	136/96 024	1.04 (0.95–1.15)	36/31 223	28/14 749	1.53	0.93–2.51	72/50 052	1.07	0.70–1.62	0.9095
Lung[b]	1137/96 024	1.04 (1.01–1.07)	222/31 223	137/14 749	1.03	0.83–1.27	778/50 052	1.10	0.94–1.28	0.1960
Breast[c]	1703/50 563	0.98 (0.95–1.01)	599/17 663	276/8547	0.95	0.82–1.10	828/24 353	0.97	0.87–1.08	0.6380
Endometrial[a]	254/32 392	0.92 (0.85–1.00)	106/10 682	36/5372	0.66	0.45–0.96	112/16 239	0.69	0.52–0.91	0.0089
Ovarian	162/50 563	1.04 (0.95–1.14)	50/17 663	30/8547	1.21	0.77–1.91	82/24 353	1.17	0.82–1.67	0.3982
Prostate	3037/46 667	0.99 (0.97–1.01)	889/13 854	417/6378	1.02	0.91–1.15	1731/26 435	1.02	0.94–1.10	0.7020
Kidney[b]	318/96 024	0.94 (0.88–1.00)	104/31 223	50/14 749	0.99	0.70–1.38	164/50 052	0.84	0.65–1.09	0.1746
Bladder[b]	398/96 024	0.99 (0.94–1.05)	92/31 223	62/14 749	1.22	0.88–1.69	244/50 052	1.08	0.85–1.39	0.6390
Glioma	103/97 334	0.89 (0.78–1.01)	38/31 547	16/14 945	0.86	0.48–1.55	49/50 842	0.76	0.50–1.17	0.2092
Thyroid	106/97 334	1.00 (0.89–1.12)	36/31 547	17/14 945	1.04	0.58–1.85	53/50 842	1.00	0.65–1.53	0.9801

Abbreviations: CI = confidence interval; PLCO = Prostate, Lung, Colorectal, and Ovarian; RR = relative risk. All RRs are adjusted for age (continuous), sex, race, and education.
[a]Additionally adjusted for smoking status (never/former/current), smoking frequency (cigarettes per day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories), and drinking frequency (drinks per day categories).
[b]Additionally adjusted for smoking status (never/former/current), smoking frequency (cigarettes per day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories).
[c]Additionally adjusted for drinking frequency (drinks per day categories).

years on birth control (<1, 2–3, 4–5, 6–9, 10+ years), number of live births, years taking female hormones (<1, 2–3, 4–5, 6–9, 10+ years), age at menopause (<40, 40–44, 45–49, 50–54, 55+ years). The RRs additionally adjusted on these BMI and reproductive factors were 0.67 (95% CI = 0.45–0.99) for drinking 1–1.9 coffee cups per day and 0.72 (95% CI = 0.55–0.95) for drinking ⩾2 coffee cups per day (*P* for trend = 0.0205).

When stratified by sex, we did not observe an association between coffee intake and the risk of cancer overall or for specific cancers. The only exception was that we observed an association between coffee intake and the risk of glioma among men. The RRs for glioma among men were 0.89 (95% CI = 0.44–1.91) for 1–1.9 cups of coffee per day and 0.53 (0.31–0.92) for drinking ⩾2 coffee cups per day (*P* for trend = 0.0219).

Tea intake, including both caffeinated and decaffeinated, was associated with a decreased risk of cancer overall (RR = 0.95, 95% CI = 0.94–0.96; Table 3). The risk of specific cancer sites, however, was not associated with tea intake. The number of cancer cases who drank coffee in the <1 cup per day groups were 3040 for all cancers, 33 for head and neck cancer, 24 for esophageal cancer, 38 for stomach cancer, 255 for lung cancer, 684 for breast cancer, 97 for endometrial cancer, 68 for ovarian cancer, 784 for prostate cancer, 88 for kidney cancer, 88 for bladder cancer, 30 for glioma, and 24 for thyroid cancer. Every one cup increase in tea consumption per day appeared to increase the risk of endometrial cancer, but comparing individuals who drank less than one cup per day *vs* one cup or more did not show any association. When stratified by sex, tea intake was not associated with any specific cancers for men or for women. The overall cancer risk for drinking 1 or more cups of tea per day was 1.03 (95% CI = 0.96–1.10) for women and 1.00 (95% CI = 0.94–1.07) for men.

When we assessed overall caffeine intake, decreased risks were observed in specific quartiles for stomach cancer, prostate cancer, and thyroid cancer; although with no dose–response (Table 4). Increased risks because of caffeine intake were also suggested for some specific quartiles for ovarian cancer and for kidney cancer, although again with no consistent dose–response.

DISCUSSION

We observed a decreased risk of endometrial cancer for women drinking 1 or more cups per day of coffee compared with those who drank less than a cup per day. Although we observed some increased and decreased risks in specific quartiles of caffeine intake, there were no dose–response trends observed, suggesting that caffeine is not the key constituent in associations between cancer and coffee or tea. Tea intake was protective against cancer overall with a 5% decrease for 1 or more cups of tea per day compared with less than 1 cup per day. However, cancer site-specific decreased risks were not significant.

Our observation of no association between coffee intake and total cancer risk is consistent with most previous studies (Malerba *et al*, 2013b). Although some studies have reported on inverse associations between coffee intake and head and neck cancer (Galeone *et al*, 2010), oesophageal squamous cell carcinoma and prostate cancer, we did not observe strong associations with coffee for these cancers. Our results also corroborate with no association of coffee intake with oesophageal adenocarcinoma (Turati *et al*, 2011), stomach (Botelho *et al*, 2006), ovarian (Steevens *et al*, 2007), kidney (Huang *et al*, 2014), thyroid cancer (Mack *et al*, 2003), and glioma (Malerba *et al*, 2013a), as reported in previous studies and meta-analyses. Although tea appeared to be protective against overall cancer in our study, cancer-specific reductions in risk were not observed.

The inverse relationship between coffee drinking and endometrial cancer may be related to various components of coffee. Besides caffeine, coffee contains more than a thousand chemicals (IARC, 1991), some of which have antioxidant and antimutagenic activities in animal models and cell culture systems (Cavin *et al*, 2002). These include several phenolic compounds (such as chlorogenic, caffeic, ferulic, and cumaric acids), melanoidins, and diterpenes (such as cafestol and kahweol; Daglia *et al*, 2000; Anese and Nicoli, 2003) whose concentration in the beverage varies depending on type of raw coffee (Arabica or Robusta), roasting, and preparation, as unfiltered coffee contains less

Table 3. Tea (caffeinated and decaffeinated) intake and cancer risk in the PLCO cohort

		<1 Cup per day	⩾1 Cup per day			
	Total cases/cohort	Per cup	Cases/cohort	Cases/cohort	RR	95% CI
All cancers[a]	10 399/96 024	1.00 (0.98–1.02)	8232/75 280	2167/20 744	0.95	0.94–0.96
Head and neck[a]	145/96 024	1.01 (0.88–1.17)	118/75 280	27/20 744	1.07	0.70–1.63
Oesophageal[a]	99/96 024	1.01 (0.84–1.20)	83/75 280	16/20 744	0.88	0.51–1.50
Stomach[a]	136/96 024	0.99 (0.85–1.16)	105/75 180	31/20 744	1.22	0.81–1.82
Lung[b]	1137/96 024	0.99 (0.95–1.04)	925/75 280	212/20 744	0.96	0.83–1.12
Breast[c]	1698/50 563	1.01 (0.97–1.05)	1252/37 917	446/12 646	1.06	0.95–1.18
Endometrial[a]	254/32 293	1.09 (1.00–1.19)	180/24 272	74/8012	1.24	0.95–1.63
Ovarian	162/50 563	0.91 (0.79–1.06)	125/37 917	37/12 646	0.87	0.60–1.26
Prostate	3037/46 667	0.98 (0.95–1.01)	2524/38 315	513/8352	0.92	0.84–1.02
Kidney[b]	318/96 024	0.98 (0.89–1.09)	246/75 280	72/20 744	1.16	0.89–1.52
Bladder[b]	398/96 024	0.97 (0.88–1.07)	326/75 280	72/20 744	0.98	0.76–1.26
Glioma	103/97 334	1.04 (0.88–1.22)	81/76 318	22/21 016	1.04	0.65–1.66
Thyroid	106/97 334	1.06 (0.91–1.22)	77/76 318	29/21 016	1.23	0.80–1.89

Abbreviations: CI = confidence interval; PLCO = Prostate, Lung, Colorectal, and Ovarian; RR = relative risk. All RRs are adjusted for age (continuous), sex, race, education.
[a]Additionally adjusted for smoking status (never/former/current), smoking frequency (cigarettes per day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories), and drinking frequency (drinks per day categories).
[b]Additionally adjusted for smoking status (never/former/current), smoking frequency (cigarettes per day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories).
[c]Additionally adjusted for drinking frequency (drinks per day categories).

Table 4. Caffeine intake and cancer risk in the PLCO cohort

		Quartiles of caffeine intake										
		Quartile 1	Quartile 2			Quartile 3			Quartile 4			
		⩽34 mg per day	34.01–266.06 mg per day			266.07–647.25 mg per day			>647.25 mg per day			
	Total cases	Cases	Cases	RR	95%CI	Cases	RR	95%CI	Cases	RR	95% CI	*P* for trend
All cancers[a]	10 399/96 024	2492/24 065	2498/24 048	1.01	0.95–1.06	2486/24 010	0.95	0.90–1.01	2923/23 901	1.05	0.99–1.11	0.2692
Head and neck[a]	145/96 024	26/24 097	20/24 048	0.68	0.38–1.22	39/24 010	1.18	0.71–1.95	60/23 901	0.89	0.55–1.44	0.9133
Oesophageal[a]	99/96 024	18/24 097	18/24 048	0.95	0.49–1.82	26/24 010	1.26	0.69–2.33	37/23 901	1.04	0.58–1.87	0.7428
Stomach[b]	136/96 024	36/24 097	37/24 048	1.03	0.65–1.63	20/24 010	0.57	0.33–0.99	43/23 901	0.86	0.54–1.37	0.2328
Lung[b]	1137/96 024	209/24 097	219/24 048	0.97	0.80–1.17	262/24 010	0.91	0.76–1.10	447/23 901	1.00	0.84–1.18	0.9335
Breast[c]	1698/50 563	488/14 799	487/14 014	1.05	0.93–1.19	526/14 931	1.04	0.92–1.18	197/6819	0.86	0.73–1.02	0.2947
Endometrial	256/32 293	72/8974	83/8844	1.18	0.86–1.62	62/9898	0.78	0.55–1.09	39/4577	1.07	0.72–1.58	0.4725
Ovarian	162/50 563	37/14 799	49/14 014	1.44	0.94–2.21	56/14 931	1.52	1.00–2.34	20/6819	1.25	0.72–2.15	0.1849
Prostate	3037/46 667	657/9515	630/10 298	0.89	0.80–1.00	651/9381	1.01	0.90–1.12	1099/17 473	0.92	0.84–1.02	0.3606
Kidney[b]	318/96 024	70/24 097	96/24 048	1.36	1.00–1.85	75/24 010	1.06	0.76–1.47	77/23 901	0.82	0.59–1.16	0.1027
Bladder[b]	397/96 024	90/24 097	76/24 048	0.83	0.61–1.13	84/24 010	0.89	0.66–1.19	147/23 901	0.91	0.69–1.19	0.1942
Glioma	103/97 334	29/24 336	23/24 331	0.82	0.47–1.42	29/24 334	1.05	0.63–1.75	22/24 333	0.68	0.38–1.20	0.3379
Thyroid	106/97 334	36/24 336	24/24 331	0.65	0.39–1.10	22/24 334	0.58	0.34–0.99	24/24 333	0.84	0.49–1.45	0.3152

Abbreviations: CI = confidence interval; PLCO = Prostate, Lung, Colorectal, and Ovarian; RR = relative risk.All RRs are adjusted for age (continuous), sex, race, education.
[a]Additionally adjusted for smoking status (never/former/current), smoking frequency (cigarettes per day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories), and drinking frequency (drinks per day categories).
[b]Additionally adjusted for smoking status (never/former/current), smoking frequency (cigarettes per day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories).
[c]Additionally adjusted for drinking frequency (drinks per day categories).

amounts of lipid component, such as diterpenes (Viani, 1993). In particular, cafestol and kahweol may reduce the genotoxicity of some carcinogens (Cavin *et al*, 2002) and may activate enzymes involved in cancerogenic detoxification (Cavin *et al*, 1998; Majer *et al*, 2005), such as glutathione *S*-transferase and ***N***-acetyltransferase (Huber and Parzefall, 2005). Still, no definite biological mechanism of the potential healthy role of coffee on endometrial cancers is available (La Vecchia and Tavani, 2007). Our results suggest that caffeine is not the component of coffee that confers a protective effect against endometrial cancer. Tea is also composed of a complex mixture including polyphenols and flavinoids, which are antioxidants (Gardner *et al*, 2007). Flavinoids may also have anti-inflammatory properties and may inhibit tumorigenesis (Gardner *et al*, 2007).

Strengths of our study are the prospective design, detailed tobacco smoking adjustments, and large sample size. As the questionnaire data were collected before cancer diagnosis, we can exclude the possibility of recall bias. We investigated cancer overall as well as specific cancer sites. We explored whether caffeine was associated with cancer risk. We reported on differences in the mean coffee intake in cups per day by age, sex, race/ethnicity, education, tobacco, and alcohol habits. As tobacco smokers had higher frequencies of coffee intake, detailed adjustment for tobacco smoking as a potential confounder was very important. The sample size of the cohort as well as the number of cancer patients was very large.

Some limitations of our study are that we did not have information on duration of coffee or tea drinking, cumulative coffee intake over the lifetime, and more details on the types of coffee (espresso, drip and so on). As the frequency of coffee and tea was captured at baseline for the last 12 months, it is possible that individuals later became coffee or tea drinkers, and we might misclassify them as non-drinkers. Conversely, individuals who were drinking coffee and/or tea at baseline may have stopped shortly before the questionnaire, in which case the coffee or tea drinking reported may not have been reflective of their usual habits over a long period of time. Although we had fairly large numbers of cancer cases, for specific subsites such as oesophageal, head and neck, and prostate cancer, we were not able to refine the groups further by histology, finer subsites or by tumour grade. In addition, multiple testing may also account for some of the associations observed, in the absence of any overall consistent trend in risk for coffee drinking. Also, we adjusted for education as a potential confounder as an indicator of socioeconomic status, but we cannot rule out the possibility that there is still confounding because of socioeconomic status or related health behaviours.

In summary, we observed a decreased risk of endometrial cancer for coffee intake and a decreased risk of cancer overall associated with tea intake. Future studies capturing the age at starting coffee and tea intake, and time periods of changes in habit (increase or decrease) would be useful.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Anese M, Nicoli MC (2003) Antioxidant properties of ready-to-drink coffee brews. *J Agric Food Chem* **51**: 942.

Bai Y, Yuan H, Li J, Tang Y, Pu C, Han P (2014) Relationship between bladder cancer and total fluid intake: a meta-analysis of epidemiological evidence. *World J Surg Oncol* **12**: 223.

Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams-Campbell LL, Rosenberg L (2010) Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. *Cancer Causes Control* **21**: 1941.

Bohn SK, Blomhoff R, Paur I (2014) Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. *Mol Nutr Food Res* **58**: 915.

Botelho F, Lunet N, Barros H (2006) Coffee and gastric cancer: systematic review and meta-analysis. *Cad Saude Publica* **22**: 889.

Braem MG, Onland-Moret NC, Schouten LJ, Tjønneland A, Hansen L, Dahm CC, Overvad K, Lukanova A, Dossus L, Floegel A, Boeing H, Clavel-Chapelon F, Chabbert-Buffet N, Fagherazzi G, Trichopoulou A, Benetou V, Goufa I, Pala V, Galasso R, Mattiello A, Sacerdote C, Palli D, Tumino R, Gram IT, Lund E, Gavrilyuk O, Sánchez MJ, Quirós R, Gonzales CA, Dorronsoro M, Castaño JM, Gurrea AB, Idahl A, Ohlson N, Lundin E, Jirstrom K, Wirfalt E, Allen NE, Tsilidis KK, Kaw KT, Bueno-de-Mesquita HB, Dik VK, Rinaldi S, Fedirko V, Norat T, Riboli E, Kaaks R, Peeters PH (2012) Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. *Am J Clin Nutr* **95**: 1172.

Bravi F, Bosetti C, Tavani A, La Vecchia C (2009a) Coffee drinking and hepatocellular carcinoma: an update. *Hepatology* **50**: 1317.

Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, Tavani A (2009b) Coffee drinking and endometrial cancer risk: a meta-analysis of observational studies. *Am J Obstet Gynecol* **200**: 130.

Cao S, Liu L, Yin X, Wang Y, Liu J, Lu Z (2014) Coffee consumption and risk of prostate cancer: a meta-analysis of prospective cohort studies. *Carcinogenesis* **35**: 256.

Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW, Schilter B (2002) Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem Toxicol* **40**: 1155.

Cavin C, Holzhauser D, Constable A, Huggett AC, Schilter B (1998) The coffee-specific diterpenes cafestol and kahweol protect against aflatoxin B1-induced genotoxicity through a dual mechanism. *Carcinogenesis* **19**: 1369.

Daglia M, Papetti A, Gregotti C, Berte F, Gazzani G (2000) In vitro antioxidant and ex vivo protective activities of green and roasted coffee. *J Agric Food Chem* **48**: 1449.

Discacciati A, Orsini N, Wolk A (2014) Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer–a dose-response meta-analysis. *Ann Oncol* **25**: 584.

Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J (2013) Prospective study of the relationship between coffee and tea with colorectal cancer risk: the PLCO Cancer Screening Trial. *Br J Cancer* **109**: 1352.

Folsom AR, Mckenzie DR, Bisgard KM, Kushi LH, Sellers TA (1993) No association between caffeine intake and postmenopausal breast cancer incidence in the Iowa Women's Health Study. *Am J Epidemiol* **138**: 380.

Galeone C, Tavani A, Pelucchi C, Turati F, Winn DM, Levi F, Yu GP, Morgenstern H, Kelsey K, Dal Maso L, Purdue MP, McClean M, Talamini R, Hayes RB, Franceschi S, Schantz S, Zhang ZF, Ferro G, Chuang SC, Boffetta P, La Vecchia C, Hashibe M (2010) Coffee and tea intake and risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium. *Cancer Epidemiol Biomarkers Prev* **19**: 1723.

Gardner EJ, Ruxton CH, Leeds AR (2007) Black tea–helpful or harmful? A review of the evidence. *Eur J Clin Nutr* **61**: 3.

Hirose K, Niwa Y, Wakai K, Matsuo K, Nakanishi T, Tajima K (2007) Coffee consumption and the risk of endometrial cancer: evidence from a case-control study of female hormone-related cancers in Japan. *Cancer Sci* **98**: 411.

Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, Yao XD, Zheng JH (2014) Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies. *Int Urol Nephrol* **46**: 1481.

Huber WW, Parzefall W (2005) Modification of N-acetyltransferases and glutathione S-transferases by coffee components: possible relevance for cancer risk. *Methods Enzymol* **401**: 307.

IARC (1991) Coffee, tea, mate, methylxanthines and methylglyoxal. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 27 February to 6 March 1990. *IARC Monogr Eval Carcinog Risks Hum* **51**: 1.

Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM (2008) Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. *Arch Intern Med* **168**: 2022.

Jordan SJ, Purdie DM, Green AC, Webb PM (2004) Coffee, tea and caffeine and risk of epithelial ovarian cancer. *Cancer Causes Control* **15**: 359.

Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW (2000) Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. *Int J Cancer* **88**: 313.

La Vecchia C, Tavani A (2007) Coffee and cancer risk: an update. *Eur J Cancer Prev* **16**: 385.

Lee JE, Hunter DJ, Spiegelman D, Adami HO, Bernstein L, van den Brandt PA, Buring JE, Cho E, English D, Folsom AR, Freudenheim JL, Gile GG, Giovannucci E, Horn-Ross PL, Leitzmann M, Marshall JR, Männistö S, McCullough ML, Miller AB, Parker AS, Pietinen P, Rodriguez C, Rohan TE, Schatzkin A, Schouten LJ, Willett WC, Wolk A, Zhang SM, Smith-Warner SA (2007) Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies. *Int J Cancer* **121**: 2246.

Lu Y, Zhai L, Zeng J, Peng Q, Wang J, Deng Y, Xie L, Mo C, Yang S, Li S, Qin X (2014) Coffee consumption and prostate cancer risk: an updated meta-analysis. *Cancer Causes Control* **25**: 591.

Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, Hallquist A, Jin F, Kolonel L, La Vecchia C, Levi F, Linos A, Lund E, McTiernan A, Mabuchi K, Negri E, Wingren G, Ron E (2003) A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. *Cancer Causes Control* **14**: 773.

Majer BJ, Hofer E, Cavin C, Lhoste E, Uhl M, Glatt HR, Meinl W, Knasmüller S (2005) Coffee diterpenes prevent the genotoxic effects of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and N-nitrosodimethylamine in a human derived liver cell line (HepG2). *Food Chem Toxicol* **43**: 433.

Malerba S, Galeone C, Pelucchi C, Turati F, Hashibe M, La Vecchia C, Tavani A (2013a) A meta-analysis of coffee and tea consumption and the risk of glioma in adults. *Cancer Causes Control* **24**: 267.

Malerba S, Turati F, Galeone C, Pelucchi C, Verga F, La Vecchia C, Tavani A (2013b) A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. *Eur J Epidemiol* **28**: 527.

Michels KB, Holmberg L, Bergkvist L, Wolk A (2002) Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women. *Ann Epidemiol* **12**: 21.

Millen AE, Tooze JA, Subar AF, Kahle LL, Schatzkin A, Krebs-Smith SM (2009) Differences between food group reports of low-energy reporters and non-low-energy reporters on a food frequency questionnaire. *J Am Diet Assoc* **109**: 1194.

Najem GR, Louria DB, Seebode JJ, Thind IS, Prusakowski JM, Ambrose RB, Fernicola AR (1982) Life time occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. *Int J Epidemiol* **11**: 212.

Slattery ML, West DW (1993) Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States). *Cancer Causes Control* **4**: 559.

Song YJ, Kristal AR, Wicklund KG, Cushing-Haugen KL, Rossing MA (2008) Coffee, tea, colas, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **17**: 712.

Steevens J, Schouten LJ, Verhage BA, Goldbohm RA, Van Den Brandt PA (2007) Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. *Br J Cancer* **97**: 1291.

Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, McIntosh A, Rosenfeld S (2001) Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. *Am J Epidemiol* **154**: 1089.

Sun CL, Yuan JM, Koh WP, Yu MC (2006) Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis* **27**: 1310.

Thompson FE, Subar AF, Brown CC, Smith AF, Sharbaugh CO, Jobe JB, Mittl B, Gibson JT, Ziegler RG (2002) Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. *J Am Diet Assoc* **102**: 212.

Turati F, Galeone C, La Vecchia C, Garavello W, Tavani A (2011) Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies. *Ann Oncol* **22**: 536.

Tworoger SS, Gertig DM, Gates MA, Hecht JL, Hankinson SE (2008) Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer. *Cancer* **112**: 1169.

Viani R (1993) The composition of coffee. In *Caffeine, Coffee and Health*, Garattini S (ed). Raven Press: New York.

Wu S, Li F, Huang X, Hua Q, Huang T, Liu Z, Liu Z, Zhang Z, Liao C, Chen Y, Shi Y, Zeng R, Feng M, Zhong X, Long Z, Tan W, Zhang X (2013) The association of tea consumption with bladder cancer risk: a meta-analysis. *Asia Pac J Clin Nutr* **22**: 128.

Zhong S, Chen W, Yu X, Chen Z, Hu Q, Zhao J (2014) Coffee consumption and risk of prostate cancer: an up-to-date meta-analysis. *Eur J Clin Nutr* **68**: 330.