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

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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.
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 decaffeinated 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., 2014), or thyroid cancer (Mack et al., 2012). 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 2001. 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=9763) 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 (Dominiani 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, 1,137 lung cancers, 1,703 breast cancers, 257 endometrial cancers, 162 ovarian cancers, 3,037 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 7,601. 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, 5,243 were in the control arm and 5,156 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 χ² 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 χ² = 0.0411), and endometrial cancer (0.3% of control group and 0.23% of intervention group were diagnosed; P-value for χ² = 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...”
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            | 10 089 | 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              | 5306   | 5.2        | 2.3                                  | 0.65                           | 598    | 5.8                                 | 2.2    | 0.57                                 |
| 6–10             | 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 = 0.41–1.10) 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) | Total cases/cohorts | <1 Cup per day | 1–1.9 Cups per day | ≥2 Cups per day | P for trend |
|-----------------------------------------------|---------------------|----------------|-------------------|----------------|-----------|
|                                               |                     | Cases/cohorts | Cases/cohorts | Cases/cohorts | RR | 95% CI | Cases/cohorts | RR | 95% CI |     |
| All cancers*                                   | 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*                                | 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*                                  | 99/96,024           | 1.03 (0.92–1.15) | 22/31,223      | 23/14,749     | 1.06–3.43 | 54/50,052 | 0.93 | 0.56–1.56 | 0.4746 |
| Stomach                                       | 136/96,024          | 1.04 (0.95–1.15) | 36/31,223      | 28/14,749     | 0.93–2.51 | 72/50,052 | 1.07 | 0.70–1.62 | 0.9095 |
| Lung*                                         | 1137/96,024         | 1.04 (1.01–1.07) | 222/31,223     | 137/14,749    | 1.03 | 0.83–1.34 | 778/50,052 | 1.10 | 0.94–1.28 | 0.1960 |
| Breast*                                       | 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*                                  | 254/32,392          | 0.92 (0.85–1.00) | 106/10,682     | 36/5372       | 0.66 | 0.45–0.94 | 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*                                       | 318/96,024          | 0.94 (0.88–1.00) | 104/31,223     | 50/14,749     | 0.97 | 0.70–1.38 | 164/50,052 | 0.84 | 0.65–1.09 | 0.1746 |
| Bladder*                                      | 398/96,024          | 0.99 (0.94–1.05) | 92/31,223      | 62/14,749     | 0.88–1.69 | 244/50,052 | 0.84 | 0.85–1.39 | 0.6390 |
| Glialma                                       | 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     | 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.

*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).

**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).

**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.

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

| Cancer Site         | Total cases/cohort | Per cup | Cases/cohort | Cases/cohort | RR     | 95% CI   |
|---------------------|--------------------|---------|--------------|--------------|--------|----------|
| All cancers         | 10 397/96 024      | 1.00 (0.98–1.02) | 8232/75 280 | 2167/20 744 | 0.95   | 0.94–0.96 |
| Head and neck       | 145/96 024         | 1.01 (0.88–1.17) | 118/75 280 | 27/20 744   | 1.07   | 0.70–1.63 |
| Oesophageal         | 99/96 024          | 1.01 (0.84–1.20) | 83/75 280 | 16/20 744   | 0.88   | 0.51–1.50 |
| Stomach             | 136/96 024         | 0.99 (0.85–1.16) | 105/75 180 | 31/20 744   | 1.22   | 0.81–1.82 |
| Lung                | 1137/96 024        | 0.99 (0.95–1.04) | 925/75 280 | 212/20 744  | 0.96   | 0.83–1.12 |
| Breast              | 1698/50 563        | 1.01 (0.97–1.05) | 1252/37 917 | 446/12 646 | 1.06   | 0.95–1.18 |
| Endometrial         | 254/32 293         | 1.09 (1.00–1.19) | 180/24 272 | 74/80 12   | 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            | 300/76 4667        | 0.98 (0.95–1.01) | 252/38 315 | 51/83 52   | 0.92   | 0.84–1.02 |
| Kidney              | 318/96 024         | 0.98 (0.89–1.09) | 246/75 280 | 72/20 744  | 1.16   | 0.89–1.52 |
| Bladder             | 396/96 024         | 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 | 22/210 16  | 1.04   | 0.65–1.66 |
| Thyroid             | 106/97 334         | 1.06 (0.91–1.22) | 77/76 318 | 29/210 16  | 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.

aAdditionally 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).

bAdditionally 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 BMI (continuous categories).

cAdditionally 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 reproductive factors (continuous categories).

dAdditionally 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 BMI (continuous categories).

eAdditionally 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 BMI (continuous categories).

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 (Malerb 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 (Malerb 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), melanoids, 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...
amounts of lipid component, such as diterpenes (Viani, 1993). In particular, cafestol and kahweol may reduce the genotoxicity of some carcinogens (Cavin et al., 1998; Majer et al., 2005), such as glutathione S-acetyltransferase (Huber and Farzefal, 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 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.

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.

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