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Dietary consumption of tea and the risk of prostate cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

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Abstract:

Tea contains polyphenols such as flavonoids, anthocyanidins, flavanols and phenolic acids which in laboratory studies have reported to promote antioxidant enzyme formation, reduces excess inflammation, slow cancer cell proliferation and promote apoptosis. Evidence from epidemiological studies, on the effect of tea consumption on CaP incidence has been conflicting. We analysed data from 25 097 men within the intervention arm of the 155000 participant Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial screening trial. Histologically confirmed cases of prostate cancer were reported in 3,088 men (12.3%) during the median 11.5 year follow up. Tea consumption was assessed with a food frequency questionnaire. Baseline characteristics were compared between groups using Chi-square and Kruskal-Wallis tests. Cox regression models were used to assess associations between tea intake and CaP incidence. There was no statistical difference between the risk of CaP between men who never drank tea to those who drank tea at any quantity. Amongst tea drinkers, those in the highest third of consumption group had a small but significantly lower risk compared to those in the lowest third (11.2% v 13.2% HR 1.16; 95% CI 1.05-1.29, $p=0.004$). This pattern persisted with adjustments for demographics and lifestyle. In conclusion, among tea drinkers, there was a small positive association between drinking tea and a reduced risk of prostate cancer. It does not support starting to drink tea, if men previously did not, to reduce the risk. Further research is needed to establish whether tea is justified for future prospective nutritional intervention studies investigating CaP prevention.

Introduction

Tea, brewed from leaves of the leaves of the *Camellia Sinensis* bush is the most popular beverage worldwide, after water. Tea may be categorised as black, green or oolong- depending the method of production. Thought to have been consumed since 2700 BC, tea has a long cultural history of being thought of as health drink (1). Prostate cancer has the highest incidence of all cancers in men, and is a prominent cause of cancer mortality (2). There is considerable interest in exploring the impact of the widely consumed beverage tea, on men's risk of this common cancer.

Research interest in the potential anti-cancer benefits of tea centres on its rich content of flavonoid polyphenols, a plant-derived micronutrient group (1). The notable flavonoid polyphenols in tea catechin, epicatechin, epigallocatechin-3-gallate and proanthocyanidins (3–5). The flavonoids in tea have been proposed to have anti-cancer benefits (6). Whilst flavonoids do possess some anti-oxidant activity, this is not thought to be significant in vivo in the context of other more potent redox influencers (6). The potential anti-cancer properties of tea are instead thought to include modulation of cell signalling pathways for oncogenic transformation, inflammation, apoptosis and angiogenesis (5,7,8).

Clinical intervention studies in patients with a range of different cancers have involved small sample groups, but have demonstrated good tolerability in some indication of possible clinical benefit. A phase II trial in 42 patients from the Mayo Clinic, administered a green tea extract to patients with previously untreated Chronic Lymphocytic Leukaemia (CLL) (9). In this single arm study 15 patients experienced a >20% reduction in lymphocyte count. Additionally, 11 out of 12 patients with palpable lymphadenopathy had at least a 50% reduction in palpable lymph node volume. There have also been a few studies examining green tea supplementation in established prostate cancer. A phase II single arm study of 26 men administered green tea extract in the median 34 day interval between diagnosis with localised prostate cancer and radical prostatectomy (10). Despite the short treatment duration there was a mean 10.4% decrease in PSA ($p=0.012$). The double blind UK National Cancer Research Network (NCRN) pomi-T randomised 203 men with localised prostate cancer 6 months of either placebo or a supplement containing green tea extract, as well as extracts from other polyphenol rich foods (pomegranate, broccoli and turmeric) (11). Men in the treatment group experienced a significantly lower median PSA rise (difference 63.8% ANCOVA, $P=0.0008$).

In light of this emerging evidence for possible clinical activity of green tea in prostate cancer there is considerable interest in whether there is a role for the prevention of prostate cancer. A recently updated Cochrane review conducted a meta-analysis of clinical intervention studies of green tea supplementation for the prevention of prostate cancer (12). Three studies, small preventative benefit were reported but the conclusion was this was of low certainty, due to the small sample sizes. These studies also included men with a high risk of prostate cancer due to existing pre-malignant histological abnormalities. In our dataset men did not have pre-existing risk factors so is a better representation of the general population.

Epidemiological studies have linked a reduced risk of breast and prostate cancer with long term tea intake, although the results are not all consistent (2,11,13). The 2006 Ohsaki prospective cohort study of 40,530 people in Japan reported that green tea consumption reduced all cause mortality but found no association with cancer mortality (14). The 2020 Cochrane review of epidemiological studies linking green tea consumption with cancer risk concluded that there is insufficient evidence for a benefit or risk (12). The review also examined prostate cancer risk in relation to green tea intake, encompassing 13 studies with 127,239 participants. The finding was of a reduced relative risk, but the authors acknowledged the further confirmatory research was needed because that despite the large effect size, there were inconsistencies that rendered this result very low confidence. For these reasons, together with the popularity of tea drinking and high incidence of prostate cancer, it was deemed necessary to conduct this new analysis specifically looking at tea intake.

The Prostate, Lung, Colorectal and Ovarian (PLCO) Trial, was a large scale randomised control trial of screening by the US National Cancer Institute (NCI) (15). PLCO datasets, which include dietary data have been a rich resource for epidemiological studies (16,17).

Methods. We analysed data from 25,097 men out of 49 104 men and women enrolled to the intervention arm of the intervention arm of the 155 000 participant PLCO screening trial who were recruited from 10 screening centres across the U.S. between November 1993 and July 2001.

Baseline characteristics were determined for the men in intervention cohort (n=25097) (tables 1). For the analysis concerned with the relationship between tea consumption and prostate cancer incidence, subjects were excluded if did not complete the baseline questionnaire, were not asked to

complete the Dietary Questionnaire (DQX) at baseline, completed the DQX but determined to be invalid, were not followed up after the enrolment or had cancer prior to enrolment in the PLCO study.

Histologically confirmed cases of prostate cancer were reported in 3,088 men (12.3%) during a median 11.5 year follow up. Tea consumption was assessed with a dietary questionnaire which assessed food frequency and was completed at the time of randomisation the intervention arm. Men were split into tertiles (T) according to dietary intake of tea drinks assessed by weight in grams per day. Daily tea consumption in T1, T2 and T3 was estimated to be 1.81-21.74g, 22.05-219.2g, 258.2-4632.23g respectively. The FFQ is a 137-item food frequency questionnaire developed to assess usual diet consumption during the past year. Dietary intake of energy and nutrients were calculated by multiplying the amount of energy and nutrients in a standard portion size of each food item by the reported frequency of consumption. The questions related to tea drinking included hot tea, iced tea and whether decaffeinated or caffeinated with 10 categories of intake..

The vast majority (96.8%) of the PLCO participants completed the baseline questionnaire that solicited information on age, ethnicity, body mass index (BMI, kg/m²), education level, physical activity, cigarette smoking, family history of prostate and other cancers, vegetable and total energy intake.

Men in the intervention arm were offered annual prostate-specific antigen (PSA) blood test and digital rectal exam (DRE) for screening prostate cancer during their first 6 years of participation in the trial and follow-up continued for at least 7 additional years. Any diagnosis of cancer was reported in the clinical research folder whether detected by screening in the first 6 years or clinically for the next 7 years. In this follow up period, men were referred for diagnostic evaluation including a prostate biopsy, if they had a PSA test >4 ng/mL or if they had nodularity, induration, asymmetry, or a loss of anatomic landmarks of the prostate on digital rectal examination. During a median follow up of 11.5 years, 3,088 cases of any grade of prostate cancer were identified from the 25,097 eligible men.

Statistical analysis: Demographic, anthropometric and lifestyle characteristics of subjects were compared across tertiles of total tea intake and the no tea intake group using the Chi-square test or Fisher's Exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Monotonic trend (upward or downward) across groups was assessed using linear regression for continuous variables and the Cochran-Armitage test for categorical variables. Between-group

baseline differences were also examined between subjects who developed any prostate cancer and those who were free from this malignancy during the specified follow-up period, using the Chi-square test or Fisher's Exact test for categorical variables and the Student's T-test or Wilcoxon Mann-Whitney test for continuous variables.

Cox proportional hazards regression models were used to assess the association between tea intake and prostate cancer incidence, both unadjusted and sequentially adjusting for demographics, history of cancer, lifestyle and diet characteristics that were shown to be significantly different between tea intake groups. Hazard ratios, 95% confidence intervals and p-values were presented for each tea intake group (including the non-tea drinkers group) compared against the reference group (no intake T=0, with the other categories of tea intake (Table 2). Among tea drinkers the lowest tertile (T=1) was compared to the highest tea intake tertile (T3) (Table 3). All statistical analyses were performed using R Version 3.6.2.

Results

The baseline characteristics (Table 1) showed there were statistically significant between-group differences ($p < 0.001$) found in age, ethnicity, BMI, smoking, exercise levels, educational level, alcohol consumption and energy intake according to level of tea intake. Higher tertile tea drinkers, were more likely to be of Asian ethnicity, have a higher overall energy intake, lower levels of alcohol consumption and were more likely to have never smoked. As expected, total caffeine intake, was higher among those in the upper tertile of tea drinkers. No significant difference was found in family history of cancer between groups. These factors were taken into account in the adjusted survival analysis.

Of the 4863 men who never drank tea 565 (11.6%) developed CaP and of the 5913 men who were in the upper tertile of tea intake 664 (11.2%) developed CaP. Using the Cox proportional hazards regression models, men who never drank tea had no greater risk of prostate cancer to men in the upper tertile of tea intake (11.6% v 11.2% HR 0.96, SD 0.86 - 1.08, $p = 0.501$) (Table 2). Likewise there was no statistical difference, after adjustment for demographics and lifestyle between non-tea drinkers. low and moderate intake tea drinkers (T1 and T2 groups), see table 3.

Of the 20234 men who drank tea, 849 of 6444 (13.2%) developed CaP in the lower tertile of tea drinkers and 664 of 5913 (11.2%) in the upper tertile of tea intake. Using the Cox proportional hazards regression models, there was a statistically significant difference of 13.2% v 11.2% HR 1.16;

95% CI 1.05-1.29, $p=0.004$). This pattern persisted with adjustments for demographics of age, race and education level (T1vT3, $p=0.012$); family history of cancer ($p=0.020$); lifestyle habits of smoking, BMI, caffeine and alcohol consumption ($p=0.038$); and other dietary factors of calorific intake ($p=0.020$), see table 3.

Conclusions

In this large prospective cohort study, we found that there was no difference in the risk of prostate cancer between men who did not drink tea and those who drank the low, moderate or highest quartile of tea intake. The data suggests that tea drinkers can be reassured that they can continue to enjoy this popular beverage without increasing their risk of CaP. Among tea drinkers there was a significant inverse association of tea consumption with the risk of prostate cancer. These associations were independent of established or suspected risk factors for prostate cancer and differences in baseline characteristics. The effect of tea consumption among the lowest and highest consumers of tea drinkers was, however, small (mean 2% difference), so although statistically significant, because of the large numbers in this data set, it is debatable whether this is clinically relevant. Also, as the dataset only specifically screened for CaP in the first 6 years of the study for those who presented clinically thereafter a potential of detection bias cannot be excluded.

Another potential weakness of this study is that, the DQX did not differentiate between black tea and green tea, or ask about the strength of the tea or the brands used, all of these variables can significantly affect the levels of these polyphenols. Tea brands can also vary in the age of the leaves taken from the bush, with the upper-most, younger tips being richest in polyphenols (21). Moreover, according to the USDA Database for the Flavonoid Content of Selected Foods, brewed tea can deliver ten times more than bottled green tea (17). With this variability in mind, it is difficult to estimate the quantity of polyphenols within each group in this dataset. In terms of quantity of tea cups consumed, based on a g:ml conversion of 1:1 the lowest tertial would be approximately one cup of brewed tea 2-4 days a week and for the upper tertial 4-10 large cups a day or up to 8 pitchers of ice tea.

A further potential limitation of this present study is that dietary intake of tea was estimated using a food frequency questionnaire at baseline, dietary habits could have changed the subsequent years of follow up. It is also well known that recall errors often occur in questionnaire based dietary assessment. If non-differential, could result in an attenuation of the strength of the associations of interest. What's more, the bioavailability of ingested polyphenols can be influenced by host factors

such as bacterial microflora in the gut (22) and the combination with other polyphenol rich foods such as turmeric, broccoli and pomegranate which is known to have significant synergistic influence on biological processes which could affect cancer initiation and progression (11,23,24)

This data adds weight to the discussion concerning tea consumption and prostate cancer but is by no means conclusive. Considering these factors, this data does not suggest that starting to drink tea, among previous non-tea drinkers would be useful preventative strategy against CaP. Moving forward further prospective intervention studies are required to ascertain whether higher tea take could have a role in prostate cancer incidence. Clearly any dietary interventions should consider healthy lifestyle along with fruit, vegetables, fibres and phytochemical rich foods (18–20). In view of the uncertainties of polyphenol content in tea as a beverage, concentrated tea, in supplement form, may aid the design, standardisation and control of a randomised trial. Likewise, it would be prudent to investigate the combination of tea with other polyphenol rich whole foods bearing in mind, results from previous intervention studies. Our trial group, is planning a preventative study, in higher risk men in the near future.

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Conflict of interest

The authors declare no competing financial interests

Author Contributions

RT directed and devised the study. Prepared the draft manuscript. BG contributed to interpreting results, updated results tables, contributed a literature search and prepared the final manuscript. AM Main statistical analyser. BS Head of Statistical analysis and overall lead. MW Administrative head of the study - data co-ordination and registration

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Table 1 Baseline characteristics of study participants split into tertiles (T) according to dietary intake of Tea (g/day) during the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO).

		Total Tea Intake (g/day)				p-value
		(0.0)	T1 (>0.0-22.04)	T2 (22.05-263.61)	T3 (263.62-4632.23)	
Eligible Participants	N	4863	6444	7877	5913	-
	N (N missing)	4863 (0)	6444 (0)	7877 (0)	5913 (0)	
Age at study entry, in years	Mean (SD)	62.2 (5.3)	63.0 (5.2)	62.5 (5.2)	62.5 (5.3)	p ¹ <0.001
	Median (IQR)	61.0 [58.0, 66.0]	63.0 [59.0, 67.0]	62.0 [58.0, 66.0]	62.0 [58.0, 66.0]	p ² =0.001
	[Min, Max]	[55.0, 74.0]	[55.0, 74.0]	[55.0, 75.0]	[55.0, 74.0]	
	N (N missing)	4863 (0)	6444 (0)	7877 (0)	5913 (0)	
Ethnicity	N (%) White, Non-Hispanic	4639 (95.4%)	5995 (93.0%)	7103 (90.2%)	5289 (89.4%)	p ¹ <0.001
	N (%) Black, Non-Hispanic	81 (1.7%)	166 (2.6%)	244 (3.1%)	125 (2.1%)	p ² <0.001
	N (%) Hispanic	76 (1.6%)	110 (1.7%)	125 (1.6%)	95 (1.6%)	
	N (%) Asian	44 (0.9%)	136 (2.1%)	348 (4.4%)	356 (6.0%)	
	N (%) Other	23 (0.4%)	37 (0.5%)	57 (0.7%)	48(0.8%)	

BMI, in kg/m ²	N (N missing)	4819 (44)	6382 (62)	7785 (92)	5857 (56)	
	Mean (SD)	27.8 (4.1)	27.4 (3.9)	27.5 (4.0)	27.6 (4.2)	p ¹ <0.001
	Median (IQR)	27.3 [25.1,	26.8 [24.7,	26.9 [24.8,	27.0 [24.7, 29.7]	p ² =0.038
	[Min, Max]	30.0]	29.5]	29.6]	[15.2, 54.5]	
		[15.1, 51.8]	[16.4, 59.6]	[15.4, 66.3]		
Education Level	N (N missing)					
	N (%) Less Than 8 Years	4861 (2)	6435 (9)	7867 (10)	5908 (5)	
	N (%) 8-11 Years	62 (1.3%)	44 (0.7%)	47 (0.6%)	44 (0.7%)	
	N (%) 12 Years Or Completed High School	479 (9.9%)	410 (6.4%)	336 (4.3%)	280 (4.7%)	
	N (%) Post High School Training Other Than College	1197 (24.6%)	1269 (19.7%)	1260 (16.0%)	914 (15.5%)	p ¹ <0.001
	N (%) Some College	672 (13.8%)	862 (13.4%)	928 (11.8%)	690 (11.7%)	p ² <0.001
	N (%) College Graduate	908 (18.7%)	1258 (19.5%)	1592 (20.2%)	1188 (20.1%)	
	N (%) Postgraduate	751 (15.4%)	1245 (19.3%)	1657 (21.1%)	1233 (20.9%)	
		792 (16.3%)	1347 (20.9%)	2047 (26.0%)	1559 (26.4%)	
Smoking Status	N (N missing)	4863 (0)	6444 (0)	7873 (4)	5912 (1)	
	N (%) Never	1870 (38.5%)	2251 (34.9%)	3044 (38.7%)	2372 (40.1%)	p ¹ <0.001
	N (%) Former	2406 (49.5%)	3491 (54.2%)	4134 (52.5%)	3048 (51.6%)	p ² =0.228
	N (%) Current	587 (12.1%)	702 (10.9%)	695 (8.8%)	492 (8.3%)	

Table 1 (continued) Baseline characteristics of study participants split into tertiles (T) according to dietary intake of Tea (g/day) during the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), 1993-2009.

		Total Tea Intake (g/day)				
		(0.0)	T1 (>0.0-22.04)	T2 (22.05-263.61)	T3 (263.62-4632.23)	p-value
Smoking Pack Years	N (N missing)	4809 (54)	6353 (91)	7780 (97)	5839 (74)	
	Mean (SD)	25.5 (32.2)	24.6 (30.0)	21.9 (28.6)	21.6 (28.7)	p<0.001
	Median (IQR)	14.0 [0.0, 42.0]	15.0 [0.0, 39.0]	11.0 [0.0, 36.0]	10.0 [0.0, 36.0]	p=0.364
	[Min, Max]	[0.0, 230.0]	[0.0, 260.0]	[0.0, 230.0]	[0.0, 210.0]	
Physical Activity Level (Moderate or Strenuous)	N (N missing)					
	N (%) None or < 1 Day/Week	3691 (1172)	4833 (1611)	6031 (1846)	4452 (1461)	
	N (%) 2-3 Days/Week	1885 (51.1%)	2611 (54.0%)	3063 (50.8%)	2260 (50.8%)	p<0.001
	N (%) 4-5 Days/Week	1321 (35.8%)	1655 (34.2%)	2281 (37.8%)	1619 (36.4%)	p=0.578
	N (%) 6-7 Days/Week	358 (9.7%)	392 (8.1%)	536 (8.9%)	420 (9.4%)	
	N (%) 8-9 Days/Week	127 (3.4%)	175 (3.6%)	151 (2.5%)	153 (3.4%)	
	N (%) 10-14 Days/Week					

Alcohol Intake (mg/Day)	N (N missing)	4863 (0)	6444 (0)	7877 (0)	5913 (0)	
	Mean (SD)	16.1 (31.7)	17.0 (30.1)	15.8 (25.7)	13.9 (25.5)	p<0.001
	Median (IQR)	2.6 [0.0, 19.2]	4.1 [0.5, 22.9]	4.9 [0.6, 21.6]	2.7 [0.4, 16.9]	p<0.001
	[Min, Max]	[0.0, 380.2]	[0.0, 394.9]	[0.0, 369.6]	[0.0, 380.8]	
Caffeine Intake (mg/Day)	N (N missing)	4863 (0)	6444 (0)	7877 (0)	5913 (0)	
	Mean (SD)	519.2 (690.3)	580.9 (670.6)	543.3 (596.8)	579.6 (614.8)	p<0.001
	Median (IQR)	369.7 [32.2, 664.7]	376.3 [149.1, 673.1]	388.7 [156.7, 672.4]	425.7 [200.1, 707.5]	p<0.001
	[Min, Max]	[0.0, 3521.0]	[0.8, 3520.6]	[3.7, 3399.4]	[43.4, 4015.5]	
Total Energy Intake (kcal/Day)	N (N missing)	4863 (0)	6444 (0)	7877 (0)	5913 (0)	
	Mean (SD)	2294.3 (834.9)	2282.2 (819.4)	2328.0 (814.4)	2447.5 (860.2)	p<0.001
	Median (IQR)	2165.4 [1698.9, 2758.0]	2156.6 [1697.5, 2732.7]	2215.0 [1742.4, 2792.2]	2323.5 [1819.1, 2944.6]	p<0.001
	[Min, Max]	[777.8, 5549.3]	[773.1, 5591.6]	[780.7, 5550.1]	[779.7, 5580.6]	
Family History of any Cancer	N (N missing)	4856 (7)	6430 (14)	7870 (7)	5898 (15)	
	N (%) Yes	2588 (53.3%)	3444 (53.6%)	4096 (52.0%)	3056 (51.8%)	p=0.124
	N (%) No	2268 (46.7%)	2986 (46.4%)	3774 (48.0%)	2842 (48.2%)	p=0.036

Table 2: Survival Analysis results for the incidence of prostate cancer diagnosis across range of tea intake (g/day). The categorical cox regression model presents the hazard ratio (HR), 95% confidence interval (CI) and corresponding p-value for lowest tertile tea intake group with the reference group comprising those consuming the highest level of tea (T3=258.2 - 4632.23g tea/day). The overall p-value presents the overall level of association between tea intake and the lower incidence of prostate cancer diagnosis

Categorical Model	Tea Intake Group	Cases / CaP (%)	HR	95% CI	P-value
Unadjusted	T1 v T3	849/6444 (13.2%) v 644 / 5913 (11.2%)	1.16	1.05-1.29	p=0.004
Adjusted for demographics ¹	T1 v T3	3083/25071 (12.3%)	1.13	1.02-1.25	p=0.012
Adjustments for family history of cancer ²	T1 v T3	3083/25035 (12.31%)	1.13	1.02-1.25	p=0.020
Adjustments for lifestyle ³	T1 v T3	3044/24784 (12.28%)	1.12	1.01-1.24	p=0.038
Adjustments for energy intake ⁴	T1 v T3	3044/24784 (12.28%)	1.11	1.0- 1.23	p=0.020

1 = age, sex, race and education level; 2 = family history of cancer; 3 = smoking, BMI, physical activity levels, caffeine and alcohol consumption; 4 = energy intake, T1 = 1.81-21.7423g tea/day, T3=258.2-4632.23g tea/day).

Table 3: Survival Analysis results for the incidence of prostate cancer diagnosis across range of tea intake (g/day). The categorical cox regression model presents the hazard ratio for each tertile group of tea intake with the reference group comprising those consuming 0g tea per day. The overall p-value presents the overall level of association between tea intake and the lower incidence of prostate cancer diagnosis.

Categorical Model	Tea intake group ⁴	Cases / Cap (%)	HR	95% CI	P value
Unadjusted	T0 v T1:	3088/25097 (12.3%)	1.12	1.00-1.24	p=0.040
Unadjusted	T0 v T2:	3088/25097 (12.3%)	1.10	0.99-1.21	p=0.083
Unadjusted	T0 v T3:	3088/25097 (12.3%)	0.96	0.86-1.08	p=0.501
Adjusted for demographics ¹	T0 v T1:	3053/24727 (12.35%)	1.08	0.97-1.20	p=0.173
Adjusted for demographics ¹	T0 v T2:	3053/24727 (12.35%)	1.08	0.97-1.20	p=0.160
Adjusted for demographics ¹	T0 v T3:	3053/24727 (12.35%)	0.95	0.85-1.07	p=0.393
+ Adjustments for dietary information ²	T0 v T1:	3053/24727 (12.35%)	1.08	0.97-1.21	p=0.147
+ Adjustments for dietary information ²	T0 v T2:	3053/24727 (12.35%)	1.08	0.98-1.20	p=0.132
+ Adjustments for dietary information ²	T0 v T3:	3053/24727 (12.35%)	0.96	0.86-1.08	p=0.499

¹ Unadjusted model;

² Model adjusted for demographics - age, sex, race, smoking status, cigarette pack-years, education, family history of cancer;

³ Model further adjusted for dietary information - alcohol use, energy (kcal) intake, red meat intake, fruit intake, caffeine intake.

⁴ T1 = 1.81-21.7423g tea/day, T2 = 22.05-219.2 g tea/ day, T3=258.2-4632.23g tea/day).