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Coffee Intake and Risk of Colorectal Cancer Among Chinese in Singapore: The Singapore Chinese Health Study

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Abstract

We prospectively investigated whether coffee consumption was associated with decreased risk of colorectal cancer and whether cigarette smoking and stage of disease modify the association in the Singapore Chinese Health Study. During the first 12 years of follow-up, 961 colorectal cancer cases occurred in the cohort of over 60,000 middle-aged or older Chinese men and women living in Singapore. Baseline dietary exposures were assessed through in-person interviews using a validated food frequency questionnaire. The relation between coffee consumption and colorectal cancer risk was assessed by proportional hazards (Cox) regression. No overall association between coffee intake and colorectal cancer was observed. However, in analysis by subsite and stage restricted to ever smokers, the coffee–colon cancer association became statistically significant for advanced disease (P for trend = 0.01). The hazard ratio was 0.56 (95% confidence interval = 0.35–0.90) for advanced colon cancer in drinkers of 2 or more cups per day compared with those who drank no coffee or less than 1 cup per day. Although there is a null association between coffee intake and risk of colorectal cancer overall, coffee may protect against smoking related advanced colon cancer.

INTRODUCTION

Heterocyclic aromatic amines (HAA) are implicated in the development of colorectal cancer, one of the most common cancers worldwide (1). Meats cooked at high temperatures are typically considered primary HAA sources. Coffee and its components, specifically the diterpenes cafestol and kahweol, mitigate the genotoxicity of HAA in vitro and in animal

models (2–4). A commonly consumed beverage, coffee has thus been studied for chemoprotective effects in humans. The results of epidemiologic studies have been somewhat inconsistent (see review by Tavani and La Vecchia [5]); however, a meta-analysis suggested an inverse association between coffee intake and risk for colorectal cancer across most case-control studies, whereas prospective studies were inconclusive (6).

Most of the current epidemiologic data were derived from studies of North American or European Whites and thus may be influenced by inherent confounders associated with the Western lifestyle. Furthermore, the method of coffee preparation can significantly influence the levels of potentially chemoprotective compounds in coffee. Instant, filtered, and percolated coffee have negligible amounts of cafestol and kahweol; whereas espresso has intermediate amounts; and Turkish, cafetière, and Scandinavian-type boiled coffees have large amounts (7). The Singapore Chinese are a useful population for overcoming these potential limitations in the current literature because 1) they are culturally and genetically distinct from the much-studied North American and European Whites, and 2) Singaporeans primarily drink coffee made from dark roasted beans with the coffee usually strained through a muslin bag to separate it from the grounds. Due to significant trapping of cafestol and kahweol in paper filters (8,9), it is assumed that these two compounds are present in significant amounts in common Singapore coffee. We previously reported that cigarette smoking, but not diet, may be a major source of HAA exposure in Asian Chinese (10). Furthermore, cigarette smoking has been observed to be a significant risk factor for colorectal cancer (primarily rectal cancer) in Singapore Chinese (11). Hence, the primary objectives of this analysis were 1) to assess the relation between coffee intake and colorectal cancer risk in this unique population; 2) to assess if the coffee-disease association differ by subsite (colon vs. rectum); 3) to assess the potential modifying effect of cigarette smoking on the coffee–colorectal cancer association; and 4) to assess if the coffee–colorectal cancer association differs by the duration of follow-up. Based on the well-established hypercholesterolemic effect of cafestol and kahweol (12,13), we further tested if coffee intake is associated with elevated level of cholesterol in our study population in order to support the assumption that cafestol and kahweol (the putative chemoprotectants in coffee) are present in Singapore coffee.

SUBJECTS AND METHODS

Study Population

The subjects were participants of the Singapore Chinese Health Study, a population-based, prospective investigation of diet and cancer risk (14). The cohort is drawn from permanent residents or citizens of Singapore who reside in government housing estates (86% of Singaporeans resided in such facilities during the enrollment period). We restricted study subjects to the two major dialect groups of Chinese in Singapore: the Hokkien, who originated from southern Fujian province, and the Cantonese, who came from central Guangdong province (these are contiguous provinces in Southeastern China). The eligible age range for cohort enrollment was 45–74 yr. Between April 1993 and December 1998, 63,257 subjects (~85% of eligible subjects) were recruited. The mean age of cohort subjects at enrollment was 56.5 yr. Among cohort participants, 1,936 subjects were excluded due to history of cancer diagnosis at baseline. Thus, this study included 61,321 subjects. The study was approved by the Institutional Review Boards of both the National University of Singapore and the University of Minnesota.

Baseline Interview

At recruitment, each subject was interviewed in person by a trained interviewer using a structured questionnaire. The questionnaire elicited demographic information, lifetime

tobacco use, current physical activity profile, occupational exposure, medical history, family history of cancer, and menstrual and reproductive history (women only). Dietary information (frequency and portion size) during the past 12 months also was obtained using a 165-item food frequency questionnaire (FFQ). The FFQ was subsequently validated for intake of various food items including alcoholic and nonalcoholic beverage against a series of 24-h dietary recalls (14). Daily intakes of about 100 nutritive/nonnutritive dietary components were computed via linkage of the FFQ response to the Singapore Food Composition Table that we developed in conjunction with the Singapore cohort study (14).

For coffee intake, study subjects were asked to choose their intake frequency during the past 12 months from 9 predefined categories: never or hardly ever, 1 to 3 times a month, once a week, 2 to 3 times a week, 4 to 6 times a week, once a day, 2 to 3 times a day, 4 to 5 times a day, and 6 or more times a day. Study subjects who smoked at least one cigarette a day for 1 yr or longer were classified as “ever” smokers and otherwise defined as “never” smokers.

Blood Collection and Lipid Measurement

One year after recruitment began, we started to collect blood (20 ml) and single-void urine samples from a random 3% sample of the cohort participants. Most blood samples were collected in the morning, and not all participants fasted. Information on the time of last meal was recorded. The blood specimens were kept immediately in dry ice after collection and transported to the Community, Occupational and Family Medicine Department, National University of Singapore, where various components of blood (plasma, serum, red blood cells, and buffy coat) were separated before they were stored at -80°C until analysis.

Direct measurements of total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), and triglycerides were performed in the Department of Laboratory Medicine, National University Hospital. TC and HDL-c were measured with the enzymatic, colorimetric method with sterol esterase, cholesterol oxidase, and 4-aminoantipyrine (15–17). HDL-c was measured in the supernatant after centrifugation, whereby chylomicrons and very or low density lipoprotein-cholesterol (LDL-c) were precipitated using phosphotungstic acid and magnesium ions. Triglycerides were measured using the enzymatic, colorimetric method with glycerol-3-phosphate oxidase and 4-aminoantipyrine (18). LDL-c was calculated according to the Friedewald formula whereby $\text{LDL-c} = \text{TC} - \text{HDL-c} - (\text{triglycerides}/5)$ (19).

Follow-Up

Identification of incident colorectal cancer cases and deaths among cohort members were accomplished by record linkage of the cohort data set with respective data sets from the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases (1). In our recent follow-up telephone/in-person interview conducted between 1999 and 2004, among the 61,685 subjects (97.5%) that we had contact or follow-up information—either from themselves, their next of kin or death records—only 17 subjects (0.03%) had migrated out of Singapore. This suggests that emigration is negligible among the subjects in the cohort.

Outcome Cases

As of December 31, 2005 (an average of 9.8 yr of follow-up), 969 cohort participants who were free of cancer at baseline had developed colorectal cancer. The cancer diagnoses were confirmed via manual review of pathology reports by a medically trained research staff. 945 (97.5%) colorectal cancer cases were diagnosed histologically, and remaining cases were diagnosed clinically ($n = 14$) or identified through death certificates only ($n = 10$). After

excluding 2 cases of lymphomas and 6 cases of in situ carcinomas, the analysis included 961 incident cases of invasive colorectal carcinoma.

Statistical Analysis

The χ^2 test and the analysis of variance (ANOVA) method were used to compare the distributions of selected variables across different levels of coffee consumption. For each subject, person years of follow-up were counted from the date of recruitment to the date of diagnosis of colorectal cancer, death, or December 31, 2005, whichever occurred first. Proportional hazards (Cox) regression methods were used to examine the association between coffee intake and risk of colorectal cancer (20). The proportionality assumption on the association between coffee intake and colorectal cancer risk was not rejected ($P=0.37$). The magnitude of the association was assessed by the hazard ratio (HR) and its corresponding 95% confidence interval (CI) and P value. All Cox regression models included age at recruitment (yr), gender, dialect group (Hokkien, Cantonese), year of recruitment (1993–1995, 1996–1998), level of education (no formal education, primary school, secondary or higher education), body mass index (<20, 20 to <24, 24 to <28, 28+ kg/m²), cigarette smoking (never, light, heavy smokers), alcohol consumption (nondrinker, <7 drinks/week, 7+ drinks/week) (11), history of diabetes (no, yes) (21), family history of colorectal cancer (no, yes), weekly moderate physical activities (no, yes), and green tea intake (less than weekly, weekly, daily) (22). The heavy smokers were those who started to smoke before 15 yr of age and smoked 13 or more cigarettes per day, whereas all remaining ever smokers were defined as light smokers (11). The linear trend tests were based on the ordinal values of the coffee intake frequency categories (less than daily, 1 cup/day, and 2+ cups/day). Analyses were performed for men and women separately and for both sexes combined. The exposure and colorectal cancer risk associations that were studied were comparable between men and women. Further adjustment for total calories and fat did not materially alter the coffee and colorectal cancer risk association. Therefore, all of the presented results are for both sexes combined with adjustment for gender but without adjustment for total calories and fat.

We used analysis of covariance (ANCOVA) method (23) to examine the association between coffee intake and level of plasma lipids. The distributions of TC, LDL-c, HDL-c, TC/HDL-c ratio, and individual nutrient levels were skewed toward high values and were corrected to a large extent by transformation to naturally logarithmic values. Thus, geometric means and their 95% CIs are presented. The multivariate regression models included the following covariates: age; sex; dialect group; body mass index; cigarette smoking; consumptions of alcohol, green tea, fat, and total calories; moderate physical activity; and time interval between last meal and blood draw.

Statistical computing was conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC) statistical software package. All P values quoted are 2-sided, and P values of less than 0.05 were considered statistically significant.

RESULTS

Of the 61,321 cohort members, approximately one-third consumed 1 cup of coffee per day and another one-third consumed 2 or more cups of coffee a day, whereas the remaining one-third did not drink coffee or drank less frequently (Table 1). Men consumed more coffee than women. Cantonese drank slightly less coffee than Hokkiens. Cigarette smokers or alcohol drinkers were more likely to drink coffee. Daily coffee drinkers had lower levels of education and physical activity than those who consumed less coffee. The prevalence of diabetes was lower (7.1%) in subjects who consumed 2 or more cups of coffee than those with less than 1 cup/day (10.8%).

Among the 961 colorectal cancer cases, 591 were colon cancer and 370 were rectal cancer cases. By stage, 229, 325, and 37 colon cancer cases were at localized (Duke A and B), advanced (Duke C and D), and unknown stage at the time of cancer diagnosis, respectively. The corresponding figures for rectal cancer by stage were 147, 202, and 21, respectively.

The association between coffee consumption and colon cancer risk is presented in Table 2. Overall, there was no association between coffee intake and colorectal cancer among cohort subjects. Among ever smokers, consumption of 2 or more cups of coffee per day was associated with a statistically significant reduction in risk of advanced colon cancer (HR = 0.56, 95% CI = 0.35–0.90, *P* for trend = 0.01), but not for localized colon cancer, as compared with less than 1 cup of coffee per day. The HRs were comparable for advanced distal and proximal colon cancer (HR = 0.51, 95% CI = 0.27–0.95 for distal cancer; HR = 0.54, 95% CI = 0.24–1.24 for proximal cancer). Among never smokers, coffee drinking was neither related to localized nor advanced colon cancer risk. The interaction effect on risk of advanced colon cancer between coffee consumption and smoking was statistically significant (*P* = 0.009).

We further examined the association between coffee intake and colon cancer by duration of follow-up (median follow-up for cases was 5.7 yr). The inverse association between coffee intake and risk of advanced colon cancer among current smokers was slightly stronger in subjects with 5+ yr of follow-up (HR = 0.53, 95% CI = 0.28–0.99) than those with <5 yr of follow-up (HR = 0.89, 95% CI = 0.56–1.41), but their difference was not statistically significant (*P* = 0.78).

We repeated the analysis similarly for rectal cancer. There was no association between coffee intake and risk of rectal cancer in all subjects or those stratified by smoking status. Coffee drinking was not associated with either localized or advanced stage of rectal cancer (Table 3).

In order to confirm our assumption that common Singapore coffee is rich in cafestol and kahweol, the putative chemoprotectants with known hypercholesterolemic effects, we further examined whether coffee intake was associated with increased plasma cholesterol. There was a statistically significant positive association between coffee intake and plasma cholesterol in a random sample of our cohort subjects (see Appendix). For total cholesterol and LDL-c, *P*_{trend} was 0.015 and 0.005, respectively.

We also examined and found no difference in the coffee and colon cancer association between men and women. Among smokers, the HRs (95% CI) for advanced colon cancer associated with 2+ cups/day of coffee were 0.55 (0.33–0.93) for men and 0.63 (0.17–2.41) for women as compared with less than 1 cup of coffee per day.

DISCUSSION

In light of the recent identification of cigarette smoking as a major source of HAA in Asian Chinese and the predominance of coffee and colorectal cancer data from studies of Caucasians, we investigated the coffee and colorectal cancer association in smokers enrolled in the Singapore Chinese Health Study. In ever smokers only, there was an inverse association between coffee intake and advanced colon cancer.

That the protective effect of coffee against colon cancer is seen only in ever smokers, and for advanced disease, may be explained by an HAA-detoxification model as follows. Stir frying, usually for a relatively short time period with marinated meats, is by far the most common method of cooking in a Chinese cuisine. Multiple studies have shown that these dishes have relatively low levels of HAA (10,24,25). In contrast, we previously showed that

cigarette smoking correlates significantly with urinary 2-amino-9*H*-pyrido[2,3-*b*]indole (AaC), a potentially carcinogenic HAA, in a dose-dependent manner among Shanghai Chinese, thus suggesting smoking as a major source for this HAA in Chinese (10). Very few subjects in the same study were positive for urinary 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) or 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) (10), HAA that are often found in well done meats, which is consistent with the data cited above regarding negligible levels of HAA in Chinese cooked meats. AaC has been shown to be a colon-specific mutagen in the Big Blue mouse model (26). Furthermore, coffee that is not paper filtered is rich in the diterpenes cafestol and kahweol. These constituents increase the activities of the HAA detoxifying enzymes UDP-glucuronosyl transferases and glutathione *S*-transferases, decrease the activity of the HAA activating enzymes *N*-acetyltransferase and sulfotransferases, and decrease HAA-mediated genotoxicity in vitro and in rats (2–4,27–29). Additionally, cafestol and kahweol have demonstrated antioxidant properties in vitro and induce in rats γ -glutamylcysteine synthetase, the rate limiting enzyme in glutathione synthesis (30,31). Human studies indicate that consumption of Italian-style coffee (or espresso) increases plasma glutathione and unfiltered French press coffee increases glutathione content in colorectal mucosa (32,33). Thus, coffee that is rich in cafestol and kahweol may exert a chemopreventive effect through optimizing HAA metabolism and detoxification and/or through enhancing antioxidant capacity and reducing proliferation. Furthermore, that the protective association was seen only for colon and not rectal cancer is consistent with mice data showing that cafestol reduces synthesis of bile acids (promoters of colon cancer) by downregulating expression of cholesterol 7 α -hydroxylase, sterol 12 α -hydroxylase, and Na(+)-taurocholate cotransporting polypeptide (5,34).

It is also possible that constituents other than cafestol and kahweol are exerting chemoprotective effects. Coffee is a rich source of phenolic acids, flavonoids, and melanoidins, many of which have demonstrated antioxidant properties that can depend on degree of roasting (35–37). Smoking can increase vulnerability to oxidative stress. We reported previously that current smokers of the Singapore Chinese Health Study consumed a significantly lower amount of dietary antioxidants (38); hence, presumably smokers would derive more beneficial effects from coffee through its antioxidative properties. Additionally, in vitro data suggest that chlorogenic and caffeic acids found in coffee may decrease proliferation, cell invasion, angiogenesis, and metastasis (39–42), which could provide a biological rationale for the protective effect observed here for advanced and not localized disease. The latency period of colon cancer could be decades long. In other words, the clinical manifestation of colon cancer would be 20 to 30 years after initiation of carcinogenesis. Exposure to coffee or its constituents might more commonly occur after initiation; therefore, the protective effect of coffee on early stage of colon cancer may be less relevant than later stage cancer through its inhibition on cell invasion, angiogenesis, and metastasis.

The presence of cafestol and kahweol in coffee is dependent on the method of preparation. Scandinavian boiled, French press (i.e., plunger or cafetière coffee), and Turkish/Greek coffees have the highest amounts of the diterpenes, espressos intermediate amounts, and instant and drip-filtered coffees have negligible amounts (paper filters retain the lipid fraction released during brewing) (7,9). In Singapore, dark roasted coffee is commonly prepared by boiling in a muslin bag, a method presumed to preserve cafestol and kahweol levels. Due to the hypercholesterolemic effect of these diterpenes (43), the positive association between coffee intake and plasma cholesterol in our cohort supports our assumption that the diterpenes are present in the coffee commonly consumed by cohort subjects. The levels of cafestol and kahweol that exert putative chemopreventive activities may be lower than the levels needed to increase cholesterol (44).

Most case-control studies have reported inverse associations between coffee intake and colorectal cancer, whereas results from prospective cohort studies, which are fewer in number, have not been consistent (5,6,45,46). Most of these studies were in North American, Scandinavian, and European Whites, for which coffee consumption is high and risk profiles for colorectal cancer differ from Asian populations. In our study population, one-third of the cohort did not drink coffee on a daily basis, one-third drank approximately 1 cup per day, and the remaining one-third drank 2 or more (average 2.8) cups of coffee per day. This distinct pattern of coffee consumption in our study population provided more power for comparison between the exposure groups. Three other prospective cohort studies on coffee and colorectal cancer in Asian populations, all conducted in Japanese, were recently published. Two of the studies reported an inverse association between coffee intake and colon cancer, but only in women and they had relatively smaller numbers of cases (47,48); the third found no association for colorectal cancer or either subsite in women or men (49). All 3 studies may be subject to the limitations of filtered coffee preparation (50), whereas a unique characteristic of our study is the diterpene-preserving method of coffee preparation common in Singapore.

The chief limitation of the present study was relatively small sample sizes in subgroup analysis. There existed the possibility of chance finding given the multiple comparisons and stratification analysis. Other limitations include single administration of the diet and lifestyle questionnaire at baseline. Thus, changes in habits during follow-up are not captured. However, a relatively stronger association of coffee intake with longer term follow-up (5+ yr) than with shorter follow-up (<5 yr) suggests that random change in coffee drinking had no impact on the coffee-colon cancer association since undifferential misclassification of coffee drinking would have diluted the effect more so in the later years than earlier years of follow-up. Additionally, although our hypothesis is that unfiltered coffee protects against smoking-related colon cancer due to the action of cafestol and kahweol, we did not actually measure the levels of these constituents in coffee samples that would be representative of what is commonly consumed in Singapore. The observed increase in plasma cholesterol levels with increased coffee intake in our cohort does support the notion that these constituents are present, however. Another limitation, as inherent in any observational study, is the residual confounding on the observed coffee and colon cancer association. Therefore, the findings of this study should be interpreted with caution and need to be confirmed in future studies. In addition, future studies that not only assess the amount of coffee consumed, but also the type of coffee, the method of preparation of the coffee, and contents of cafestol and kahweol are warranted to shed light on the role of coffee in the protection against the development of colorectal cancer.

There are several strengths to our study. Information on coffee consumption and other dietary and lifestyle factors were collected prior to cancer diagnosis, thus ruling out the possibility of recall bias and reverse causality, especially when there was a stronger coffee and colon cancer association with longer than with shorter follow-up. Subgroup analyses in ever smokers were biologically driven given the recent identification of cigarette smoking as the more likely source of HAA than diet in Chinese. The study population is genetically homogeneous and free of potential confounders that may be inherent in widely studied White populations. Finally, Singapore Chinese prepare coffee in a way that likely preserves the putative chemoprotectants that have been the primary focus of basic science investigations of coffee and cancer prevention.

In summary, although the present study showed an overall null association between coffee intake and colorectal cancer risk among Chinese in Singapore, coffee, in particular, cafestol and kahweol, may protect against the development of smoking-related advanced colon cancer.

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TABLE 1

Distributions of selected baseline characteristics across categories of coffee intake in the Singapore Chinese Health Study^a

Variable	No. of Cups of Coffee/Day			P Value ^b
	<1	1	2+	
No. of subjects	18,149	22,087	21,085	
Age at baseline (yr)	56.5 ± 8.3	56.7 ± 8.0	56.0 ± 7.7	<0.001
Body mass index (kg/m ²)	23.2 ± 3.3	23.2 ± 3.2	23.0 ± 3.3	<0.001
Sex				
Male	43.0	38.2	52.4	<0.001
Female	57.0	61.8	47.6	
Dialect group				
Cantonese	47.5	47.0	44.2	<0.001
Hokkien	52.5	53.0	55.8	
Education				
No formal education	24.6	29.1	27.3	<0.001
Primary school	42.0	44.4	46.5	
Secondary or higher	33.4	26.5	26.2	
Smoking status				
Never smokers	77.0	73.5	58.8	<0.001
Light smokers	20.6	23.4	35.6	
Heavy smokers	2.4	3.1	5.6	
Alcohol status				
Nondrinker ^c	84.0	81.8	77.5	<0.001
<7 drinks/wk	12.5	13.7	16.5	
7drinks/wk	3.5	4.5	6.0	
Green/black tea intake				
Nondrinker	54.9	58.1	62.9	<0.001
Monthly	11.4	11.9	11.3	
Weekly	18.5	17.6	15.7	
Daily	15.2	12.4	10.1	
Moderate activity				
No	63.2	68.7	68.5	<0.001
Yes ^d	36.8	31.3	31.5	
Family history of colorectal cancer				
No	97.8	97.9	97.8	0.728
Yes	2.2	2.1	2.2	
Diabetes				
No	89.2	90.9	92.9	<0.001
Yes	10.8	9.1	7.1	

^aValues are means ± SD or %.

^bBased on analysis of variance for age and body mass index and chi-square test for all remaining variables.

^cDefined as <1 drink/mo.

^dModerate activities included brisk walking, bowling, bicycling on level ground, tai chi, or chi gong.

TABLE 2

Coffee intake and hazard ratios (HR) and confidence intervals (CI) for colon cancer by stage and smoking status in the Singapore Chinese Health Study

No. Cups Coffee/Day by Smoking Status	No. Person Years (N = 599,761)	All Colon Cancer Cases		Localized Colon Cancer Cases		Advanced Colon Cancer Cases	
		No. of Cases (N = 591)	HR (95% CI)	No. of Cases ^a (N = 229)	HR (95%) ^b	No. of Cases ^a (N = 325)	HR (95% CI) ^b
All subjects							
<1	174,393	177	1.00	77	1.00	91	1.00
1	216,219	228	1.04 (0.85–1.26)	77	0.88 (0.58–1.10)	140	1.25 (0.95–1.62)
2+	209,149	186	0.90 (0.73–1.11)	75	0.82 (0.59–1.14)	94	0.89 (0.66–1.19)
<i>P</i> for trend			0.31		0.24		0.40
Never smokers							
<1	136,422	125	1.00	60	1.00	57	1.00
1	161,866	147	1.00 (0.78–1.27)	50	0.71 (0.48–1.03)	90	1.34 (0.96–1.86)
2+	125,991	112	1.01 (0.78–1.31)	41	0.76 (0.51–1.14)	59	1.17 (0.81–1.70)
<i>P</i> for trend			0.93		0.15		0.38
Ever smokers							
<1	37,971	52	1.00	17	1.00	34	1.00
1	54,353	81	1.13 (0.79–1.60)	27	1.17 (0.63–2.15)	50	1.07 (0.69–1.66)
2+	83,157	74	0.77 (0.54–1.11)	34	1.11 (0.61–2.01)	35	0.56 (0.35–0.90)
<i>P</i> for trend			0.10		0.79		0.01

^a A total of 37 colon cancer cases with unknown stages were excluded from these analyses.^b Adjusted for age at baseline, gender, dialect group, year of recruitment, level of education, body mass index, cigarette smoking (for all subjects only), alcohol consumption, physical activity, history of diabetes, family history of colorectal cancer, and green tea intake.

TABLE 3

Coffee intake and hazard ratio (HR) and confidence intervals (CI) for rectal cancer by stage and smoking status in the Singapore Chinese Health Study

No. of Cups of Coffee/Day by Smoking Status (N = 599,761)	No. of Person Years	All Rectal Cancer Cases		Localized Rectal Cancer Cases		Advanced Rectal Cancer Cases	
		No. of Cases (N = 370)	HR (95% CI)	No. of Cases ^a (N = 147)	HR (95% CI) ^b	No. of Cases ^a (N = 202)	HR (95% CI) ^b
All subjects							
<1	174,393	103	1.00	45	1.00	49	1.00
1	216,219	125	0.98 (0.75–1.28)	43	0.76 (0.50–1.16)	77	1.29 (0.90–1.85)
2+	209,149	142	1.06 (0.81–1.37)	59	0.96 (0.64–1.43)	76	1.24 (0.86–1.79)
<i>P</i> for trend			0.66		0.91		0.28
Never smokers							
<1	136,422	63	1.00	28	1.00	32	1.00
1	161,866	63	0.88 (0.62–1.25)	19	0.59 (0.33–1.06)	41	1.14 (0.72–1.82)
2+	125,991	55	1.02 (0.76–1.63)	18	0.72 (0.40–1.32)	35	1.32 (0.81–2.14)
<i>P</i> for trend			0.96		0.24		0.27
Ever smokers							
<1	37,971	40	1.00	17	1.00	17	1.00
1	54,353	62	1.12 (0.75–1.67)	24	1.01 (0.54–1.89)	36	1.54 (0.86–2.74)
2+	83,157	87	1.12 (0.76–1.63)	41	1.23 (0.69–2.19)	41	1.26 (0.71–2.24)
<i>P</i> for trend			0.72		0.42		0.61

^aWe excluded 21 rectal cancer cases with unknown stages from these analyses.

^bAdjusted for age at baseline, gender, dialect group, year of recruitment, level of education, body mass index, cigarette smoking (for all subjects only), alcohol consumption, physical activity, history of diabetes, family history of colorectal cancer, and green tea intake.

Geometric means [95% confidence interval (CI)] of plasma lipids by coffee intake among 873 cohort participants in the Singapore Chinese Health Study

APPENDIX

Geometric Mean (95% CI) ^a					
Coffee Intake (No. Cups/Day)	Subjects	Total Cholesterol (mmol/l)	HDL-c ^b (mmol/l)	Total Cholesterol/HDL-c Ratio	LDL-c ^c (mmol/l)
<1	253	5.55 (5.41–5.67)	1.37 (1.33–1.41)	4.06 (3.92–4.20)	3.25 (3.13–3.37)
1	329	5.64 (5.53–5.76)	1.36 (1.33–1.40)	4.14 (4.02–4.27)	3.39 (3.28–3.50)
2–3	258	5.67 (5.54–5.80)	1.39 (1.35–1.43)	4.09 (3.95–4.23)	3.40 (3.28–3.53)
4+	33	6.21 (5.82–6.63)	1.35 (1.25–1.47)	4.59 (4.17–5.05)	3.96 (3.58–4.39)
P _{trend}		0.015	0.59	0.23	0.005

^a Adjusted for age at blood sample collection, sex, dialect group, level of education, body mass index, cigarette smoking, alcohol consumption, physical activity, history of diabetes, green tea drinking, consumptions of total fat and total calories, and the time interval between the last meal and blood draw.

^b High-density lipoprotein cholesterol.

^c Low-density lipoprotein cholesterol.