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Coffee and Tea Intake and Risk of Incident, Sporadic Colorectal
Adenomas

By

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Master of Public Health

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Coffee and Tea Intake and Risk of Incident, Sporadic Colorectal
Adenomas

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2014

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Abstract

Coffee and Tea Intake and Risk of Incident, Sporadic Colorectal Adenomas
By Junjie Guo

Background: Coffee and tea are commonly consumed beverages that contain several bioactive compounds, and have been suggested to influence colorectal carcinogenesis. However, the findings from epidemiologic studies are inconsistent.

Objective: The current study aimed at investigating the association of coffee and tea intake with risk of incident, sporadic colorectal adenomas (CRA).

Methods: We analyzed data from a case-control study conducted in the Minneapolis metropolitan area between 1991 and 1994. Participants were residents aged 30-74 years and with no personal history of colorectal neoplasms, including 564 cases, 1202 endoscopy-negative controls and 535 frequency-matched community controls. The consumption of caffeinated coffee, decaffeinated coffee and tea was analyzed as categorical and continuous variables, and the associations were estimated using unconditional logistic regression models.

Results: High intake of caffeinated coffee was associated with high risk of CRA when comparing cases with endoscopy controls (4-6 cups/day vs. nondrinkers OR=1.87 95% CI: 1.35-2.59, $P_{\text{for trend}} < 0.01$), but not with community controls (4-6 cups/day vs. nondrinkers OR=1.37, 95% CI: 0.94-1.98, $P_{\text{for trend}} = 0.17$). Decaffeinated coffee was associated with a higher risk of CRA in the comparison of cases with both endoscopy controls (2-6 cups/day vs. nondrinkers OR=1.53, 95% CI: 1.13-2.08, $P_{\text{for trend}} < 0.01$) and community controls (2-6 cups/day vs. nondrinkers OR=1.44, 95% CI: 1.01-2.04, $P_{\text{for trend}} = 0.04$). These associations were suggestively stronger for people who were overweight or obese, and who had multiple adenomas or tubular adenomas. Tea was not associated with risk of CRA.

Conclusion: Our findings suggest that high consumption of caffeinated or decaffeinated coffee may increase risk of CRA; and intake of tea is not associated with risk of CRA.

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Background

Epidemiology of Colorectal Adenoma (CRA) and Colorectal Cancer (CRC)

With the spread of western lifestyle and the improvement in living conditions, CRC has become a prominent health problem not only in North America and Europe, but also in some less developed regions. As the World Health Organization estimates, CRC is the third most common cancer in men (746,000 cases, 10% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide [1]. In the United States, CRC is the second leading cause of cancer mortality and the third most commonly diagnosed cancer, which is estimated to account for about 50,310 deaths and 136,830 new cases in 2014 [2].

CRA is defined as a benign growth in gland-like cells of the epithelial tissue of the colon and rectum [3]. Based on 18 cross-sectional studies with the proportion of male observations ranging from 40.5% to 100% in North America, it was estimated that the pooled prevalence of all adenomas, non-advanced adenomas and advanced adenomas was 30.2%, 17.7% and 5.7% respectively [4]. The evolution of colorectal carcinomas is understood to be a multistep carcinogenesis [5], beginning with a benign adenomatous polyp that develops into an advanced adenoma with high grade dysplasia and finally develops to an invasive cancer [6]. Researchers have identified that dysplastic adenomas are the principal premalignant precursor lesions of CRC [7]. The detection of adenomas using colonoscopy contributes prominently to the prevention of CRC, as individual screening and prevention measures are planned to a large extent based on measurements of existing adenomas [8]. A high adenoma detection rate was proved to be associated with a lower risk for interval CRC, advanced-stage cancer and fatal interval cancer [9].

Adenoma can be histologically classified as conventional adenoma (tubular, tubulovillus and villus adenoma), and serrated adenoma that includes traditional serrated adenoma (TSA) and sessile serrated adenoma (SSA). Both conventional adenoma and serrated adenoma have the

potential to develop into carcinoma, and serrated adenoma may progress at a higher rate [10]. Approximately 60% of colorectal carcinomas arise from conventional adenomas via the suppressor pathway leading to microsatellite stable carcinomas, 35% of carcinomas arise from SSA via serrated pathway leading to CpG island methylated phenotype positive (CIMP+) carcinoma, and the remaining 5% of carcinomas arise from conventional adenomas caused by inherited mutations that impair DNA mismatch repair (Lynch syndrome) *via* the mutator pathway leading to CpG island methylated phenotype negative (CIMP-) microsatellite instable carcinomas [11].

Genomic instability and mutations, including chromosomal instability and microsatellite instability, play an important role in the adenoma-carcinoma sequence. Researchers found the adenoma-carcinoma sequence is initiated with the mutation or loss of the *APC* gene, following with mutations of *KRAS* in the middle of the sequence and mutations of the tumor-suppressor gene *p53* in the end, which indicates colorectal carcinogenesis involves sustained mutations and gene-activating or -inactivating events in multiple genes [12]. *APC* gene has been regarded as a gatekeeper of colorectal neoplasia, considering 60% patients with colorectal carcinoma have mutations in the *APC* gene and nearly 100% of individuals with germ-line *APC* mutations will develop colon cancer [13]. Additionally, larger genetic losses in chromosome arms like 5q, 17p and 18q are also associated with colorectal carcinogenesis [14].

Risk factors for Colorectal Neoplasms

Many studies have been conducted investigating the risk factors of colorectal carcinoma, but the results were not always consistent. One widely accepted risk factor is diet, although the specific role of many foods or nutrients in carcinogenesis remains unclear. Results of previous studies indicate fiber and whole grains are convincingly associated with a decreased risk of CRC/CRA; red and processed meat is convincingly associated with an increased risk; calcium and milk probably reduce the risk; vitamin D, fruits and nonstarchy vegetables may reduce the

risk but without statistical significance; vitamin A, C, E, selenium, total fat, and Omega-3 polyunsaturated fatty acids may have limited effects on CRC/CRA [15]. Lack of physical activity and obesity are other two factors strongly associated with colorectal carcinogenesis. A meta-analysis showed that an increase of 5 metabolic equivalent tasks (MET) h/d of total physical activity is associated with a 3% lower risk of CRC and an 8% lower risk of colon cancer.

Recreational activity with an increase of 5 (MET) hour/week can reduce the risk of colorectal and colon cancers, without sufficient evidence [16]. As for obesity, many observational studies have consistently reported a positive association between excess body weight, which is mostly defined by body mass index (BMI), and risk of CRC/CRA. By reviewing meta-analysis of prospective and case-control studies published between 1900 and 2011, researchers estimated a BMI of 30 kg/m² was associated with a 30-95% higher risk of CRC in men and 10-66% higher risk of CRC in women [17]. Family history is also an important risk factor for CRC. Individuals having a first-degree relative with CRC, and increased numbers of affected first-degree relatives influence risk much more than affected second- or third-degree relatives [18]. Many hereditary cancer syndromes, such as familial adenomatous polyposis, Gardner's syndrome, hamartomatous polyposis syndromes are significantly associated with an increased risk of CRC [19].

Coffee, Tea and Colorectal Carcinogenesis

Coffee and tea are worldwide popular beverages. Coffee is the second most consumed beverage after water, and people consume approximately 500 billion cups annually [20]. For tea, it is estimated that 3.2 million metric tons of tea leaf are manufactured annually, of which 20% is green tea and 2% is oolong, the remainder being black tea [21]. Both coffee and tea contain numerous antioxidant components and caffeine that may have effects on carcinogenesis. Previous studies indicated a weak association between high intake of coffee and a lower risk of renal, ovarian, pancreatic, esophageal, endometrial, pharyngeal and CRC [22-25], and a higher risk of breast cancer and prostate cancer [26, 27]. Epidemiologic studies also showed that high intake of

green tea was associated with a reduced risk of esophageal cancer [28], stomach cancer and liver cancer [29].

Many studies regarding the association of coffee/tea and cancer have focused on the effect of dietary polyphenols. As antioxidants, polyphenols may protect DNA from oxidative damage, inhibit the expression of mutated genes and the stimulation of enzymes promoting carcinogenesis, and promote detoxification of xenobiotics [30]. Caffeic acid and chlorogenic acid are the major phenolic compounds in coffee, and they have been reported to decrease DNA methylation *in vitro* [31]. Considering hypermethylation of DNA is an important epigenetic mechanism for silencing genes, leading to carcinogenesis [32], caffeic acid and chlorogenic acid may play a protective role in preventing cancer. Two kinds of coffee specific diterpenes -- cafestol and kahweol -- also showed anticarcinogenic properties in animal models and cell culture systems by inhibiting the enzymatic activity or reducing the expression of enzyme responsible for carcinogen activation, inducing enzymes involved in carcinogen detoxification, and stimulating intracellular antioxidant defense mechanisms [33]. Tea is a rich source of antioxidant polyphenols including flavonols, epicatechin, epigallocatechin, epicatechin-3-gallate, epigallocatechin-3-gallate (EGCG) and theaflavins [21]. Since some transformations occur in the process of fermentation, the polyphenols contained in black and oolong tea may be different from polyphenols in green tea. A cell culture study demonstrated that EGCG, which is mainly contained in green tea, significantly induced cell apoptosis and restrained the proliferation of CRC cells, indicating green tea has a chemopreventive potential in cancer chemoprevention [34]. A nested case-control study on the association of urinary biomarkers of green tea and CRC found that individuals with high prediagnostic urinary epigallocatechin levels were at significantly lower risk for developing colon cancer (highest tertile vs. undetectable OR=0.40, 95% CI: 0.19-0.83), but not rectal cancer [35].

Caffeine is another bioactive component of coffee and tea that may be associated with carcinogenesis. It was reported to be an important factor in the development of hormone-related

cancers like ovarian, endometrial and breast cancers. Caffeine may reduce free blood estrogen levels and modify gastrointestinal hormone secretion, which can have an impact on colorectal carcinogenesis [23, 36]. Additionally, a significant inverse association between caffeine and tumor development was concluded in many animal experiments. Using mice models of cancer, researchers found caffeine could promote anti-tumor immune response during tumor initiation, with the involvement of adenosine receptors that can constrain the key stages of inflammatory processes [37]. An *in vitro* study on human cells also indicated caffeine could inhibit the migration of colon cancer cells stimulated by a subgroup of adenosine receptors, resulting in the suppression of colon cancer cell growth [38]. However, many observational studies obtained inconsistent results on caffeine's effects on CRC and other cancers, possibly because of different ranges and categories of doses between studies along with how they categorized exposures. Considering coffee and tea are the major sources of caffeine in American adults' diet, approximately accounting for 70% and 12% respectively [39], it is meaningful to investigate the association between coffee and tea intake and the incidence of CRC/CRA.

The association between coffee and tea intake and the risk of colorectal neoplasms has been extensively examined in epidemiologic studies, but the results were not consistent among different populations. For coffee, Naganuma et al. (2007) found it was not associated with the risk of CRC in the general population of Japan[25], while Sinha et al. (2012) reported that coffee was associated with a decreased risk of CRC among the population of six states and two metropolitan areas of the United States[40]. In addition, a positive association was suggested in Yamada et al. (2014)'s study, which showed that increasing coffee consumption was associated with a statistically significant increase risk in colon cancer among Japanese men[41]. Most previous studies focused on CRC, instead of CRA, leading to neglect of the roles of coffee in the early stages of carcinogenesis. Similarly for tea, although many researchers stated green tea could reduce the risk of carcinoma, the results of recent epidemiologic studies on CRC and tea were not always statistically significant. A cohort study among people aged 55-74 in the US indicated high

tea intake was not associated with CRC by cancer sites and stages [42], but another case control study among people in western Australia found that consumption of one or more cups of herbal tea per week could decrease risk of distal colon cancer [43]. One potential limitation of these studies is the lack of consideration of various types of tea, as green tea and black tea may have different abilities to prevent tumor genesis.

Recently, two Japanese studies focusing on CRA as an endpoint found an inverse association between the amount of daily coffee intake and CRA[44, 45]. However, since they were conducted in an Asian country, where the daily consumption of coffee was much lower compared to western countries, the effect of high coffee intake on CRA risk was not assessed. Another disadvantage was they only focused on coffee. Our study will try to fill the gap in literature, by focusing on the effect of both coffee and tea on CRA, the precursor of CRC, in order to prevent carcinoma in an earlier stage. A broader distribution of coffee doses and a consideration of different types of coffee and tea will be used in the analysis.

Methods

Study population and data collection

This case control study was conducted in the University of Minnesota Cancer Prevention Research Unit, as part of the collaboration between the University of Minnesota (Minneapolis, Minnesota) and a large, multiclinic private gastroenterology practice – Digestive Healthcare (Minneapolis, Minnesota). The data were collected from 10 hospitals and endoscopy units in the Minneapolis metropolitan area between April 1991 and April 1994. Participants were recruited when they were scheduled the usual endoscopy to screen for gastrointestinal symptoms in community-based gastroenterology practices. Patients who were 30-74 years of age, English-speaking and free of known genetic syndromes associated with predisposition to colonic

neoplasia and had no history of ulcerative colitis, familial polyposis, Crohn's Disease, Gardner's Syndrome or cancer (except non-melanoma skin cancer) were eligible to participate in this study.

Questionnaires that collected information on demographics, diet, lifestyle, physical activity, alcohol and tobacco use, medical history, family history of colon cancer and self-reported anthropometrics were mailed before endoscopy and returned at endoscopy visit. To assess food and nutritional supplement intakes over the previous 12 months, a self-administered, 166-item modified semi-quantitative Willett food frequency questionnaire was used [46, 47]. Total energy and nutrients intakes were calculated from all food resources reported in the questionnaire, in which the food frequency categorized as "1-3 per month", "1 per week", "2-4 per week", "5-6 per week", "1 per day", "2-3 per day", "4-5 per day" and "6+ per day". Each eligible participant must have undergone a complete colonoscopy reaching cecum or a flexible sigmoidoscopy, have had all polyps removed, and be free of new diagnoses of inflammatory bowel diseases or polyps with invasive carcinoma. During the endoscopy visit, locations and in vivo sizes and shapes of all polyps were recorded on the standardized form. In order to confirm the diagnosis, a study pathologist examined histological characteristics of all polyps applying National Polyp Study diagnostic criteria[48]. Cases of this study were defined as patients with an adenomatous polyp at this colonoscopy, and endoscopy controls were defined as patients that are free of adenomatous polyps at this colonoscopy.

In addition to endoscopy controls, a group of community controls (n=535) was randomly selected from the 1991 Minnesota State Driver's License Registry and frequency-matched to the cases on age (5-year intervals), sex and zip code. The participation rate among community controls was 65%. Since participants of community controls did not get a colonoscopy or sigmoidoscopy, their current polyp status was not confirmed. Except for that, they should meet the same eligibility criteria as the endoscopy controls.

Participants who left more than 10% of the food frequency questionnaire questions blank or had total energy intakes less than 600 kcal/day or more than 5000 kcal/day were considered as

invalid responses and excluded from the analyses. The final analysis included 2301 participants, including 564 cases, 1202 endoscopy controls and 535 community controls.

Statistical analysis

Intakes of caffeinated, decaffeinated and tea in cups per days were calculated from the food frequency questionnaire. Unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95%CI) for association of daily intake of coffee/tea and CRA risk. Coffee and tea intake were analyzed as categorical and continuous (per cup of intake) variables. The cut-off points were determined based on the distributions of coffee and tea intake among community controls. In order to figure out the role of caffeine in this association, total caffeine intake was analyzed separately as a continuous (1 standard deviation = 278.3 mg/day) and categorical variable (no intake, low intake, medium intake or high intake).

According to findings from previous literature, age, sex, BMI, total energy intake, family history of colon cancer in the first-degree relative, diet fiber intake, saturated meat intake, NSAID and aspirin use, physical activities (metabolic equivalent of task (MET) – hours/week), smoking status (based on current/former/never and packs of cigarettes per year), alcohol use (servings/week), cola and diet cola intake (servings/day) were considered as potential confounding variables. Variables that have biological plausibility to be considered potential confounders, or changed the adjusted odds ratio for the primary model by more than 10% were remained in the final model. The final multivariable models included age, sex, BMI, total energy intake, family history of colon cancer in the first-degree relative, NSAID and aspirin use, physical activities, smoking status and alcohol use. Coffee, decaffeinated coffee and tea intake were analyzed together in the same model.

To assess whether the association of coffee/tea consumption with risk of CRA was modified by biologically plausible effect modifiers, we conducted analyses stratified on sex (men or women), age (≤ 54 , ≤ 63 or > 63), family history (yes or no), BMI (< 25 or ≥ 25 , according to the

WHO definition, a BMI of 25 is the cut-off point for normal weight or overweight) and smoking status (non-smoker, current smoker or former smoker). The cutoff points of stratified continuous variables were determined according to the distribution of community controls. Likelihood ratio tests were used to test statistical interactions. In addition, to assess the association based on cases' adenoma characteristics, analyses on number of adenomas (1 or >1), size of largest adenoma (<1cm or \geq 1cm) and subtypes (tubular or villous/tubulovillous) were performed separately using polytomous logistic regression models. Finally, the association of CRA and other beverages, including cola, diet cola, fruit juice and vegetable juice, were assessed in different models, in order to compare with the association of CRA and coffee/tea.

All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, North Carolina). Collinearity was examined in all models using the SAS macro %collin. All odds ratios are provided with 95% confidence intervals, and all reported p values are two-tailed.

Results

Selected characteristics of 2301 participants by case-control status are presented in Table 1. Mean age was 58.1 years (SD=9.6 years) among cases, 52.8 years (SD=11.1 years) among endoscopy controls and 57.7 years (SD=10.4 years) among community controls. The distribution of fruits, vegetables and red meat consumption, total energy intake, body mass index (BMI), Metabolic Equivalent of Task (MET) hours and education level were similar among the three groups. Compared to endoscopy and community controls, cases were more likely to be male, current or former smokers and not regular users of NSAID or aspirin, and to consume more alcohol. Coffee and tea consumption varied among cases and controls. While the largest portion of cases were participants consuming more than 4 cups coffee daily, the largest portion of either of

the control groups were participants who did not drink coffee. Cases were comprised of the larger proportion of heavy decaffeinated coffee drinkers and non-tea drinkers.

Associations between coffee/tea consumption and the risk of incident, sporadic CRA are reported in Table 2. In the age and sex adjusted model, consuming caffeinated coffee 2-3 cups per day was significantly associated with an increased risk of CRA in the comparisons involving endoscopy controls (vs. nondrinkers OR=1.64, 95% CI: 1.21-2.21, $P_{\text{for trend}} < 0.01$) but not in the comparison involving community controls (vs. nondrinkers OR=1.08, 95% CI: 0.77-1.52, $P_{\text{for trend}} = 0.02$). Consuming 4-6 cups of caffeinated coffee per day was statistically associated with higher risk in comparisons involving both endoscopy (vs. nondrinkers OR=2.07, 95% CI: 1.52-2.81, $P_{\text{for trend}} < 0.01$) and community controls (vs. nondrinkers OR=1.59, 95% CI: 1.12-2.25, $P_{\text{for trend}} = 0.02$). Similarly, consuming decaffeinated coffee 2-6 cups per day was significantly associated with higher risk of CRA among endoscopy (vs. nondrinkers OR=1.39, 95% CI: 1.03-1.87, $P_{\text{for trend}} = 0.01$) and community controls (vs. nondrinkers OR=1.46, 95% CI: 1.04-2.05, $P_{\text{for trend}} = 0.03$). For tea, participants consuming less than 1 cup per day had a significant inverse association with CRA in the comparison between cases and community controls (vs. nondrinkers OR=0.76, 95% CI: 0.58-0.99, $P_{\text{for trend}} = 0.40$). The association between tea and CRA was not statistically significant when cases and endoscopy controls were compared. Considering the limited amount of observations that were heavy tea drinkers in both control groups, there may be an association between high tea intake and low risk of CRA, although it is not statistically significant. If coffee and tea were treated as continuous variables, a significant increase in the risk of CRA was associated with caffeinated and decaffeinated coffee intake respectively in the comparisons involving both control groups, while no statistically significant association between tea intake and CRA risk was found.

Multivariable-adjusted analyses were conducted by adding additional variables, including BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, NSAID and aspirin use and physical activity, into logistic models. The association between coffee/tea and

CRA was not changed in the comparison involving endoscopy controls (caffeinated coffee: 2-3 cups/day vs. nondrinkers OR=1.63, 95% CI: 1.18-2.23; 4-6 cups/day vs. nondrinkers OR=1.87 95% CI: 1.35-2.59, $P_{\text{for trend}} < 0.01$; decaffeinated coffee: 2-6 cups/day vs. nondrinkers OR=1.53 95% CI: 1.13-2.08, $P_{\text{for trend}} < 0.01$). For community controls, the association between consumption of decaffeinated coffee and CRA risk was not altered (2-6 cups/day vs. nondrinkers OR=1.44 95% CI: 1.01-2.04, $P_{\text{for trend}} = 0.04$), while consumption of caffeinated coffee and tea was not significantly associated with CRA risk anymore (caffeinated coffee: $P_{\text{for trend}} = 0.17$; tea: $P_{\text{for trend}} = 0.37$). Because of these alterations, conclusions were made mainly based on multivariable-adjusted models.

Table 3 illustrates multivariable-adjusted analyses stratified by sex, age (≤ 54 , ≤ 63 or > 63 years), BMI (< 25 or ≥ 25), smoking status (non-smoker, current smoker or former smoker). As the results show, the association of caffeinated coffee intake with CRA risk was somewhat stronger among participants who were overweight or obese (endoscopy controls: $P_{\text{for interaction}} = 0.26$; community controls: $P_{\text{for interaction}} = 0.28$), and the association of decaffeinated coffee and tea with CRA risk was stronger among women (endoscopy controls: $P_{\text{for interaction}} = 0.71$; community controls: $P_{\text{for interaction}} = 0.14$). There were no consistent patterns of differences in odds ratios comparing cases with both control groups stratified by age and smoking status. Table 5 presents further estimation of association between coffee/tea and CRA, based on adenoma characteristics. The association between caffeinated coffee consumption with CRA was stronger among people with multiple adenomas, larger adenomas and tubular adenomas. For associations between decaffeinated coffee and tea intake and CRA, there were no clear or consistent patterns according to adenoma characteristics.

The association of caffeine intake with CRA risk was also examined, and caffeine was treated as a continuous and categorical variable respectively. The result showed the consumption of caffeine slightly increased the effect on CRA in the comparison involving endoscopy controls (continuous: OR per standard deviation increase=1.21, 95% CI:1.08-1.35; categorical: highest

quartile vs lowest quartile OR=1.45, 95% CI: 1.10-1.92, $P_{\text{for trend}}=0.01$), but had no effect in the comparison involving community controls (continuous: OR per standard deviation increase=1.04, 95% CI: 0.91-1.17; categorical: highest quartile vs lowest quartile OR=0.97, 95% CI: 0.71-1.32, $P_{\text{for trend}}=0.87$). In order to compare the association of coffee/tea with CRA risk to the association of other beverages with CRA, intake of cola, diet cola, fruit juice and vegetable juice were added in models as categorical variables. However, it showed that the association between these beverages and CRA risk were close to null and not statistically significant.

Discussion

In this case-control study analyzing the effects of coffee and tea drinking frequency on CRA among 564 CRA cases, and 1202 endoscopy controls and 535 community controls in Minneapolis metropolitan area. This study included high consumption of coffee/tea intake (6 cups per day), better examining the associations among heavy coffee/tea drinkers. In addition, the effects of caffeinated and decaffeinated coffee were analyzed separately, in order to understand whether caffeine is the component determining this association. As the results suggest, high intake of caffeinated and decaffeinated coffee may be associated with an increased risk of CRA, and this association might be stronger among people who were overweight or obese and who had multiple adenomas or tubular adenomas. Tea intake was not significantly associated with CRA risk.

Extensive epidemiologic studies were conducted to assess the associations between coffee/tea intake and CRC risk, and the results were inconsistent. Some case-control and cohort studies reported null association between coffee/tea consumption and CRC/CRA risk [25, 49], whereas other studies reported a modest but statistically significant reduction in CRC or colon cancer risk among coffee/tea drinkers [40, 43, 44]. Moreover, a cohort study and a case-control study reported coffee consumption significantly increased the risk among men [41, 50]. The

results of several meta-analyses and systematic reviews showed coffee and tea were associated with a reduced risk of CRC, under both hospital-based and population-based designs [51-53]. Specifically for coffee, researchers found evidence of the inverse association from case-control studies, but little evidence from prospective cohort studies. This discrepancy may be explained by recall bias due to the case-control design. Generally, the finding that tea intake was not associated with CRC/CRA risk in current study was consistent with several previous studies, whereas the significant positive association found in coffee was only reported in a few case-control and cohort studies [41, 50].

It is unclear why high consumption of both caffeinated and decaffeinated coffee is associated with an increased risk of CRA in our study. One possible explanation is the existence of residual confounding in the association of coffee intake with CRA risk among our study population. A large prospective cohort study investigating coffee consumption and risk of Parkinson's disease reported people with higher consumption of coffee were likely to consume more alcohol and less vitamin C or vitamin E [54], which indicated coffee consumption may be associated with unhealthy lifestyle, including other unspecific exposures. Because of these unrecognized exposures, any effects on risk of CRA may be incorrectly attributed to coffee drinking. Another explanation is the inadequate adjustment for the effect of smoking [55]. Almost all studies which regarding coffee intake and CRC risk treated smoking as a potential confounder, because high consumption of coffee was shown to be associated with smoking [56]. Furthermore, the results of multivariable adjusted analysis in this study indicated current smokers and former smokers had significantly higher risk of CRA when we compared cases with endoscopy controls (current smoker vs. non-smoker OR=2.14, 95% CI: 1.54-2.98) and community controls (current smoker vs. non-smoker OR=1.74, 95% CI: 1.20-2.53; former smoker vs. non-smoker OR=1.44, 95% CI: 1.08-1.91). If participants underreported smoking, the socially undesirable behavior, whereas accurately reported coffee consumption, the socially neutral behavior, the effect of coffee on CRA risk would be overestimated. Additionally, for decaffeinated coffee, the positive

association may be explained by a history of illness among decaffeinated coffee drinkers, as a study that collected coffee consumption data among Northern California residents during 1984 to 1985 found increased decaffeinated coffee intake was associated with the use of special diets and cardiovascular, gastrointestinal or neuropsychiatric symptoms [57]. When caffeinated coffee drinkers were diagnosed with CRA, they might switch to decaffeinated coffee, which could lead to an incorrect positive association in the data analysis.

The stratified analysis did not show a significant difference between sexes using multivariable-adjusted models in the comparison involving both endoscopy controls (caffeinated coffee: $P_{\text{for interaction}}=0.69$; decaffeinated coffee: $P_{\text{for interaction}}=0.71$; tea: $P_{\text{for interaction}}=0.19$) and community controls (caffeinated coffee: $P_{\text{for interaction}}=0.25$; decaffeinated coffee: $P_{\text{for interaction}}=0.14$; tea: $P_{\text{for interaction}}=0.51$), although some studies indicated the association for men was stronger than for women [41, 50]. This is likely due to the fact that smoking and alcohol consumption, which were considered residual confounding effects in men, were well adjusted in this study. On the contrary, BMI was found to potentially modify the association of caffeinated coffee, although the interaction of BMI and caffeinated coffee in models was not statistically significant (endoscopy controls: $P_{\text{for interaction}}=0.31$; community controls: $P_{\text{for interaction}}=0.22$). According to stratified analysis, overweight and obese caffeinated coffee drinkers had a higher risk of CRA compared to their normal or underweight counterparts in the comparison involving endoscopy controls. A positive association between adiposity and CRC was consistently demonstrated by epidemiological research, and this association was stronger in men than women [58]. According to a meta-analysis of 31 studies with 70,000 events, there was a dose-response relationship between BMI and CRC, with a 2 kg/m² increase in BMI leading to 7% increase in risk in CRC [59]. A case control study found that high BMI was associated with higher risk of large adenoma, which suggested potential of adiposity to affect early stages of colorectal carcinogenesis. The epidemiological evidence for the association between obesity and colorectal neoplasm risk is sufficient, while the obesity-related carcinogenic mechanisms underlying the

association remain unclear. Hypotheses have been suggested based on the effect of energy imbalance on insulin resistance, chronic inflammation, growth factors and steroid hormones [60]. There is an assumption that high coffee or caffeine intake may reduce appetite, leading to less energy intake and controlled weight, and cause lower risk of CRC/CRA. However, epidemiological studies did not consistently support the association between coffee intake and appetite suppression [61-63]. Caffeine has also been found to decrease insulin sensitivity and elevate plasma insulin response in several clinical trials [55]. These evidence and assumptions support the finding that being overweight and obese may interact with coffee intake and further increase the risk of CRA.

Our results on caffeine intake did not support the hypothesis that caffeine is associated with reduced risk of CRA. When caffeine was analyzed as a continuous variable and categorical variable in the multivariable adjusted models, a significant positive association was found in the comparison involving endoscopy controls (continuous: OR per standard deviation increase=1.21, 95% CI: 1.08-1.35; categorical: highest quartile vs. lowest quartile OR=1.45, 95% CI:1.10-1.92, $P_{\text{for trend}}=0.01$), but not community controls (continuous: OR per standard deviation increase=1.04, 95% CI: 0.91-1.17; categorical: highest quartile vs lowest quartile OR=0.97, 95% CI: 0.71-1.32, $P_{\text{for trend}}=0.87$). This finding is consistent with the association between caffeinated coffee and CRA risk. Considering possible behavior changes among endoscopy controls, the results obtained from community controls may better represent the association of caffeine and CRA risk, and they are consistent with findings of previous epidemiologic studies. Within a nested case-control dataset (n=3427) of a perspective cohort study among European populations found that CRC risk was not significantly associated with genotype-based *CYP1A2* and *NAT2* activity, which are involved in the metabolism of caffeine [49]. It not only suggested that caffeine metabolism does not modify the link between coffee and tea consumption and CRC risk, but also questioned the role of caffeine in colorectal carcinogenesis. Another large cohort study that used data from the Nurses' Health Study and the Health Professionals' Follow-up Study of the US also found

consumption of caffeinated coffee, caffeinated tea and caffeine were not associated with incidence of CRC [64]. However, the inverse associations between caffeine and risk of CRC suggested by experimental models are not consistent with epidemiologic evidence. Likely, the results of animal studies did not accurately describe the role of caffeine in human colorectal carcinogenesis because a considerably higher level of carcinogen and caffeine exposure was applied in animal models. The rapidly progressive tumorigenesis occurring in these models was not likely to happen on human subjects, and the metabolism of caffeine in animals may be different. Moreover, the protective effect caffeine observed in animal trials may only apply to the situation when solid tumors already exist but not to the early occurrence of tumors. This effect was associated with the subset of G-protein-coupled receptors that are activated by adenosine, which accumulates to high levels as a result of ATP reduction in hypoxic environments, which exist in rapidly growing solid tumors due to insufficient diffusion of oxygen into the tissue [37, 38, 65, 66]. Thus, although caffeine may have therapeutic potential by inhibiting the growth of colorectal tumors, it does not necessarily decrease the incidence of CRA, the precursor of CRC.

This study had several strengths. From the perspective of outcome, the provision of endoscopy and standardized pathological verification of adenomas among cases and endoscopy controls could reduce the chance of misclassification of case-control status. For exposures, dietary and lifestyle information was collected prior to endoscopy procedures, which likely reduced the possibility of recall bias. The use of well-structured questionnaires facilitated data collection of information on considerable potential covariates, making more accurate assessment on the effects of coffee and tea consumption. We examined the effects of caffeinated and decaffeinated coffee separately, ruling out the role of caffeine in the association with CRA. Compared to many coffee studies conducted among Asian populations, this study had considerably more observations with high level of caffeinated coffee consumption that allowed assessing the association for heavy caffeinated coffee drinkers. Additionally, two control groups were involved in comparison with the cases. Endoscopy controls may have had similar lifestyles

and diet to the cases or had recently changed their lifestyle because of health concerns (all of them had an indication for undergoing a colonoscopy, including abdominal pain, family history of cancer or blood in the stool). Indeed in our study, the associations observed with community controls were less prominent compared to when endoscopy controls were used, which suggest that endoscopy controls may not be the optimal group and community controls are more representative of general population. However, the adenoma status among community controls was not known, and we may expect up to 20% of them to have an adenomatous polyp. The comparison of results according to these two control groups helped to examine the validation of these findings.

One major limitation of the study was the small sample size, especially for community controls. Behavior and lifestyle may have changed among endoscopy controls, causing a biased positive association. Moreover, since data of community controls were from the 1991 Minnesota State Driver's License Registry, some undiagnosed cases may have existed, leading to an attenuated result of the association. The distributions of decaffeinated coffee and tea intake were left skewed, with a lot of non-drinkers, resulting in sparse data for heavy drinkers. In order to avoid invalid results, categories representing higher consumption were combined, so we may not be able to accurately capture the association between high consumption of decaffeinated coffee or tea and CRA risk.

In conclusion, the study suggests that heavy caffeinated and decaffeinated coffee drinkers may have an increased risk of CRA, whereas tea intake may not affect the risk of CRA. However, considering the inconsistent evidence of the association of coffee and tea with CRC/CRA and limited sample size of the current study, recognition of unknown covariates and verification of these associations need to be completed in larger studies in the future.

Public Health Implication

Our study was conducted to assess the association between coffee and tea consumption and risk of CRA. We found that tea intake was not associated with CRA risk, whereas high intake of caffeinated and decaffeinated coffee may be associated with an increased risk of CRA, and this association might be stronger among people who were overweight or obese and who had multiple adenomas or tubular adenomas. The finding of caffeinated coffee was not consistent when cases were compared with endoscopy and community controls separately.

There are several reasons for different findings among two control groups. Since all of endoscopy controls had an indication for undergoing a colonoscopy, such as abdominal pain, family history of cancer or blood in stool, behavior changes may occur in this control group due to health concerns, leading to a biased positive association. Moreover, the data were collected in 1990s, when coffee and caffeine were considered unhealthy, so avoidance of heavy coffee consumption might be associated with more health awareness and healthy lifestyles.

To further the analysis of this topic, the role of other coffee components apart from caffeine in the early stage of colorectal carcinogenesis needed to be studied, given our result that caffeine is not associated with CRA risk among general population. Compared to studies focusing on effects of caffeine metabolism on CRC/CRA risk, the amount of studies of caffeic acid, chlorogenic acid or coffee specific diterpenes is very limited. Moreover, our study indicates there may be other unspecified covariates affecting the association between caffeinated coffee intake and risk of CRA, so additional unhealthy lifestyles associated with coffee drinking or CRA need to be specified and analyzed in models.

Last, prospective cohort study may be more ideal in investigating the association between coffee and tea intake and CRA risk. Most previous studies focused on CRC risk, and recently there was only one case-control study assessing the association with CRA risk [44]. Considering the limited sample size of our study, the results needed to be validated in larger cohort studies.

Identifying modifiable risk factors for colorectal neoplasms, such as intake of coffee and tea, may contribute to CRC prevention and overall health recommendations.

Appendices

Table 1: Selected characteristics of participants in the Minnesota CPRU case-control study of incident, sporadic CRA (N=2301)

	Cases(564)		Endoscopy controls ^a (1202)		Community controls(535)	
	Mean (SD)	%	Mean(SD)	%	Mean(SD)	%
Men		61.7		38.8		55.1
Age, years	58.1(9.6)		52.8(11.1)		57.7(10.4)	
White		97.7		97.2		97.2
Education						
High school graduate and below		37.2		30.5		36.8
Trade school or business school after graduating from high school		32.3		35.4		34.0
Some college and college graduate		30.5		34.1		29.2
Family history of colorectal cancer		16.1		20.0		6.9
Body mass index(BMI) ^b , kg/m ²	27.4(4.7)		26.6(4.9)		26.8(4.5)	
Total energy intake, kcal/day	2090.7(775.7)		2002.5(718.3)		2054.5(719.2)	
Smoking status						
Non-smoker		32.5		46.4		44.1
Current smoker		20.7		13.1		15.5
Former Smoker		46.8		40.5		40.4
Total alcohol intake ^b , drinks/week	5.2(7.6)		3.6(7.8)		4.5(8.8)	
Physical activity, MET-hours/week	9.3(9.9)		8.7(8.2)		9.6(9.8)	
Regular use of NSAIDs or aspirin		29.3		42.3		30.8
Hormone replacement therapy use among women only		27.3		36.3		29.6
Red meat, servings/day	0.7(0.5)		0.6(0.5)		0.6(0.5)	
Fruits, servings/week	2.4(1.8)		2.7(1.9)		2.6(1.8)	
Vegetables, servings/week	3.6(2.2)		3.9(2.6)		3.7(2.1)	

Total alcohol intake ^c , drinks/week	5.2(7.6)	3.6(7.8)	4.5(8.8)
Caffeine intake, mg/day	326.8(296.2)	257.3(268.6)	298.4(274.3)
Coffee, servings ^d /day			
	0	25.0	35.0
	≤1	25.0	26.6
	2-3	23.6	20.9
	4-6	26.4	17.5
Decaffeinated coffee, servings ^d /day			
	0	49.7	51.3
	≤1	29.6	33.4
	2-6	20.7	15.3
Tea (non-herbal), servings ^d /day			
	0	64.4	57.7
	<1	29.6	33.5
	1-6	6.0	8.7
Cola, servings ^d /day	0.2(0.5)	0.2(0.6)	0.3(0.8)
Dietcola, servings ^d /day	0.2(0.7)	0.3(0.7)	0.3(0.8)
Fruit juice, servings ^d /day	4.7(5.3)	5.6(6.2)	5.3(5.4)
Vegetable juice ^b , servings ^d /day	0.7(1.3)	0.6(1.8)	0.8(1.6)

^aEndoscopy controls included those who did not have a polyp at colonoscopy or flexible sigmoidoscopy.

^b30 missing values for BMI, 2 missing values for total alcohol intake, 2 missing values for vegetable juice.

^cOne drink is equal to 1 1/2 oz of liquor (shot), 5 oz of wine (glass), or 12 oz of beer (can/bottle).

^dOne serving is equal to one cup.

Table 2: Age- and sex- and multivariable-adjusted associations of coffee and tea intake with incident, sporadic CRA in the Minnesota CPRU case-control study, 1991-1994

	No. of cases	Endoscopy controls ^a					Community controls				
		No. of controls	Adjusted OR ^b	95% CI	Adjusted OR ^c	95% CI	No. of controls	Adjusted OR ^b	95% CI	Adjusted OR ^c	95% CI
Regular coffee											
0	141	421	1.00		1.00		151	1.00		1.00	
≤1	141	320	1.23	0.91,1.64	1.20	0.89,1.62	133	1.17	0.84,1.64	1.11	0.78,1.56
2-3	133	251	1.64	1.21,2.21	1.63	1.18,2.23	141	1.08	0.77,1.52	0.98	0.69,1.40
4-6	149	210	2.07	1.52,2.81	1.87	1.35,2.59	110	1.59	1.12,2.25	1.37	0.94,1.98
<i>P</i> -trend			<0.01		<0.01			0.02		0.17	
Per cup increase			1.16	1.09,1.22	1.13	1.06,1.20		1.09	1.02,1.16	1.06	0.99,1.13
Decaffeinated coffee											
0	280	616	1.00		1.00		281	1.00		1.00	
≤1	167	402	0.89	0.69,1.14	0.97	0.75,1.25	165	1.09	0.82,1.45	1.11	0.83,1.48
2-6	117	184	1.39	1.03,1.87	1.53	1.13,2.08	89	1.46	1.04,2.05	1.44	1.01,2.04
<i>P</i> -trend			0.01		<0.01			0.03		0.04	
Per cup increase			1.13	1.04,1.23	1.15	1.05,1.24		1.14	1.03,1.25	1.13	1.02,1.24
Tea (non-herbal)											
0	363	694	1.00		1.00		311	1.00		1.00	
<1	167	403	0.84	0.66,1.07	0.85	0.67,1.09	188	0.76	0.58,0.99	0.82	0.62,1.07
1-6	34	105	0.70	0.46,1.08	0.73	0.47,1.14	36	0.83	0.51,1.37	0.81	0.49,1.35
<i>P</i> -trend			0.10		0.17			0.40		0.37	
Per cup increase			0.86	0.72,1.03	0.87	0.72,1.04		0.94	0.76,1.18	0.93	0.74,1.16

^aEndoscopy controls included those who did not have a polyp at colonoscopy or flexible sigmoidoscopy.

^bAdjusted for age and sex.

^cAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, NSAID and aspirin use, and physical activity

Table 3: Multivariable-adjusted association of coffee and tea intake with incident, sporadic CRA by selected risk factors in the Minnesota

Quartiles	Endoscopy controls ^a						Community controls					
	Coffee		Decaffeinated coffee		Tea		Coffee		Decaffeinated coffee		Tea	
	Adjust-ed OR ^b	95% CI	Adjust-ed OR ^c	95% CI	Adjust-ed OR ^d	95% CI	Adjust-ed OR ^b	95% CI	Adjust-ed OR ^c	95% CI	Adjust-ed OR ^d	95% CI
Sex												
Male												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.05	0.69,1.61	0.84	0.59,1.21	0.93	0.65,1.31	1.09	0.69,1.72	1.08	0.73,1.59	0.91	0.63,1.31
3	1.32	0.84,2.07	1.51	0.99,2.31	1.34	0.66,2.73	1.01	0.63,1.61	1.39	0.89,2.18	1.00	0.48,2.06
4	1.88	1.19,2.96					1.61	0.99,2.62				
<i>P</i> -trend	<i><0.01</i>		<i>0.02</i>		<i>0.50</i>		<i>0.06</i>		<i>0.11</i>		<i>0.92</i>	
Female												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.35	0.87,2.08	1.15	0.79,1.67	0.77	0.54,1.10	1.20	0.70,2.06	1.12	0.71,1.75	0.66	0.43,1.00
3	1.88	1.19,2.97	1.59	1.00,2.52	0.50	0.27,0.92	1.04	0.60,1.81	1.59	0.88,2.85	0.64	0.30,1.37
4	1.73	1.06,2.83					1.11	0.61,2.03				
<i>P</i> -trend	<i>0.02</i>		<i>0.05</i>		<i>0.04</i>		<i>0.95</i>		<i>0.14</i>		<i>0.25</i>	
<i>P</i> for interaction	<i>0.69</i>		<i>0.71</i>		<i>0.19</i>		<i>0.25</i>		<i>0.14</i>		<i>0.51</i>	
Age^e												
≤54												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.53	0.92,2.56	0.84	0.55,1.27	0.63	0.42,0.96	2.26	1.14,4.46	0.91	0.54,1.54	0.58	0.35,0.96
3	2.39	1.45,3.95	1.33	0.8,2.22	1.06	0.52,2.15	1.88	0.99,3.57	1.38	0.70,2.72	0.64	0.26,1.57
4	2.47	1.48,4.12					1.72	0.90,3.28				
<i>P</i> -trend	<i><0.01</i>		<i>0.10</i>		<i>0.92</i>		<i>0.37</i>		<i>0.16</i>		<i>0.39</i>	
≤63												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	0.88	0.50,1.55	1.17	0.73,1.89	1.07	0.70,1.67	0.88	0.47,1.67	1.19	0.70,2.01	1.04	0.65,1.68

	3	0.96	0.52,1.80	2.22	1.28,3.88	0.70	0.30,1.66	0.97	0.50,1.87	2.53	1.35,4.73	0.67	0.27,1.67
	4	1.51	0.82,2.79					1.68	0.85,3.33				
	<i>P</i> -trend	0.10		<0.01		0.36		0.06		<0.01		0.38	
	>63												
	1	1.00		1.00		1.00		1.00		1.00		1.00	
	2	1.32	0.79,2.20	1.13	0.71,1.82	0.95	0.61,1.49	0.85	0.48,1.52	1.14	0.68,1.89	0.91	0.57,1.45
	3	1.90	1.04,3.45	1.50	0.84,2.69	0.61	0.29,1.30	0.60	0.33,1.10	0.81	0.44,1.48	1.48	0.55,4.01
	4	1.92	1.01,3.65					0.97	0.48,1.96				
	<i>P</i> -trend	0.04		0.23		0.23		0.65		0.51		0.53	
	<i>P</i> for interaction	0.99		0.17		0.92		0.81		0.83		0.34	
BMI													
Normal (<25)													
	1	1.00		1.00		1.00		1.00		1.00		1.00	
	2	1.09	0.65,1.84	1.01	0.65,1.57	0.97	0.64,1.47	1.83	0.99,3.39	1.05	0.63,1.77	0.80	0.49,1.29
	3	1.25	0.73,2.14	2.10	1.24,3.55	0.54	0.26,1.13	1.37	0.74,2.57	2.09	1.12,3.87	0.44	0.18,1.11
	4	1.79	1.02,3.16					1.73	0.91,3.29				
	<i>P</i> -trend	0.03		<0.01		0.10		0.27		0.02		0.11	
	Overweight or obese (≥25)												
	1	1.00		1.00		1.00		1.00		1.00		1.00	
	2	1.24	0.86,1.80	0.99	0.72,1.35	0.77	0.57,1.05	0.89	0.58,1.37	1.15	0.80,1.63	0.78	0.56,1.10
	3	1.84	1.24,2.73	1.29	0.88,1.90	0.85	0.48,1.50	0.80	0.52,1.24	1.22	0.79,1.89	0.98	0.51,1.87
	4	1.91	1.27,2.85					1.16	0.73,1.86				
	<i>P</i> -trend	<0.01		0.16		0.56		0.51		0.35		0.85	
	<i>P</i> for interaction	0.31		0.31		0.80		0.22		0.91		0.37	
Smoking status													
Non-smoker													
	1	1.00		1.00		1.00		1.00		1.00		1.00	
	2	1.21	0.76,1.91	1.06	0.70,1.62	1.12	0.75,1.67	1.07	0.64,1.79	1.06	0.67,1.68	0.90	0.58,1.38
	3	1.28	0.77,2.14	1.30	0.77,2.21	1.02	0.52,1.99	0.82	0.47,1.43	1.35	0.74,2.47	2.30	0.98,5.40

	4	2.01	1.12,3.62					1.44	0.76,2.75				
	<i>P</i> -trend	0.03		0.31		0.98		0.49		0.30		0.07	
Current smoker													
	1	1.00		1.00		1.00		1.00		1.00		1.00	
	2	0.99	0.38,2.61	0.59	0.29,1.19	0.43	0.22,0.87	1.04	0.36,2.98	1.00	0.45,2.22	0.55	0.26,1.16
	3	1.36	0.54,3.44	0.81	0.32,2.01	0.51	0.16,1.62	1.51	0.55,4.17	1.11	0.39,3.17	0.21	0.06,0.70
	4	1.42	0.61,3.32					1.21	0.50,2.95				
	<i>P</i> -trend	0.31		0.76		0.16		0.82		0.86		0.01	
Former smoker													
	1	1.00		1.00		1.00		1.00		1.00		1.00	
	2	1.23	0.78,1.93	1.06	0.72,1.55	0.79	0.55,1.13	1.03	0.60,1.78	1.15	0.74,1.80	0.82	0.54,1.25
	3	1.95	1.21,3.15	2.03	1.31,3.14	0.66	0.33,1.35	0.85	0.49,1.49	1.59	0.96,2.65	0.57	0.25,1.32
	4	1.91	1.17,3.13					1.36	0.74,2.50				
	<i>P</i> -trend	<0.01		<0.01		0.24		0.36		0.06		0.18	
	<i>P</i> for interaction	0.81		0.74		0.43		0.65		0.78		0.09	

^aEndoscopy controls included those who did not have a polyp at colonoscopy or flexible sigmoidoscopy.

^bAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, decaffeinated coffee and tea intake, NSAID and aspirin use, and physical activity.

^cAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, coffee and tea intake, NSAID and aspirin use, and physical activity.

^dAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, decaffeinated coffee and coffee intake, NSAID and aspirin use, and physical activity.

^eAge cutpoints based on the distribution reported in the community controls.

Table 4: Multivariable-adjusted association of coffee and tea intake with incident, sporadic colorectal adenomas by adenoma characteristics in the Minnesota CPRU case-control study, 1991-1994

Quartiles	Endoscopy controls ^a						Community controls					
	Coffee		Decaffeinated coffee		Tea		Coffee		Decaffeinated coffee		Tea	
	Adjusted OR ^b	95% CI	Adjusted OR ^c	95% CI	Adjusted OR ^d	95% CI	Adjusted OR ^b	95% CI	Adjusted OR ^c	95% CI	Adjusted OR ^d	95% CI
Number of adenomas												
1												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.19	0.85,1.66	1.02	0.77,1.35	0.86	0.65,1.13	1.11	0.76,1.61	1.17	0.85,1.60	0.81	0.61,1.10
3	1.59	1.12,2.26	1.65	1.18,2.31	0.70	0.42,1.15	0.98	0.66,1.43	1.57	1.07,2.29	0.77	0.44,1.36
4	1.85	1.29,2.66					1.36	0.91,2.04				
<i>P</i> -trend	<0.01		<0.01		0.16		0.23		0.02		0.33	
>1												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.21	0.75,1.97	0.87	0.58,1.30	0.84	0.57,1.24	1.11	0.66,1.85	1.00	0.65,1.53	0.82	0.55,1.22
3	1.72	1.03,2.86	1.31	0.80,2.13	0.82	0.41,1.66	1.01	0.60,1.70	1.19	0.71,1.99	0.90	0.43,1.88
4	1.96	1.17,3.27					1.43	0.83,2.45				
<i>P</i> -trend	0.01		0.21		0.60		0.24		0.45		0.72	
Size of largest adenoma												
<1cm												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.29	0.90,1.86	0.98	0.72,1.33	1.00	0.75,1.34	1.18	0.79,1.77	1.09	0.78,1.53	0.95	0.69,1.30
3	1.69	1.15,2.48	1.46	1.01,2.12	1.01	0.61,1.66	1.02	0.67,1.53	1.34	0.89,2.02	1.10	0.63,1.93
4	1.95	1.31,2.90					1.42	0.92,2.19				
<i>P</i> -trend	<0.01		0.03		0.91		0.21		0.15		0.73	
≥1cm												
1	1.00		1.00		1.00		1.00		1.00		1.00	
2	1.03	0.65,1.63	0.82	0.56,1.22	0.72	0.49,1.05	0.96	0.58,1.57	0.96	0.63,1.45	0.69	0.47,1.03
3	1.67	1.05,2.66	1.34	0.85,2.11	0.44	0.19,0.98	0.98	0.60,1.60	1.32	0.81,2.16	0.47	0.20,1.11

4	1.56	0.96,2.53					1.21	0.72,2.03					
<i>P</i> -trend	0.02		0.13		0.03		0.44		0.21		0.05		
Subtype of the worst adenoma													
tubular													
1	1.00		1.00		1.00		1.00		1.00		1.00		1.00
2	1.44	0.97,2.14	1.00	0.72,1.40	0.94	0.68,1.29	1.34	0.86,2.07	1.12	0.78,1.61	0.86	0.61,1.22	
3	1.63	1.06,2.51	1.67	1.13,2.48	0.97	0.56,1.67	1.00	0.63,1.58	1.56	1.01,2.41	1.08	0.59,1.99	
4	2.43	1.58,3.73					1.78	1.11,2.83					
<i>P</i> -trend	<0.01		0.01		0.95		0.06		0.04		0.80		
villous/tubulovillous													
1	1.00		1.00		1.00		1.00		1.00		1.00		1.00
2	1.03	0.71,1.49	0.94	0.69,1.29	0.79	0.58,1.07	0.94	0.62,1.42	1.11	0.79,1.56	0.78	0.57,1.08	
3	1.62	1.11,2.38	1.42	0.97,2.07	0.55	0.30,1.00	0.97	0.64,1.46	1.34	0.88,2.03	0.60	0.31,1.16	
4	1.51	1.01,2.25					1.10	0.71,1.71					
<i>P</i> -trend	0.01		0.05		0.05		0.63		0.17		0.10		

^aEndoscopy controls included those who had a colonoscopy and those who had only a flexible sigmoidoscopy.

^bAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, decaffeinated coffee and tea intake, NSAID and aspirin use, and physical activity.

^cAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, coffee and tea intake, NSAID and aspirin use, and physical activity.

^dAdjusted for age, sex, BMI, family history of colon cancer, total energy intake, smoke status, alcohol intake, decaffeinated coffee and coffee intake, NSAID and aspirin use, and physical activity.

^eAge cutpoints based on the distribution reported in the community controls.

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