Research Article

Cancer Epidemiology, Biomarkers & Prevention

Coffee Consumption and the Risk of Colorectal Cancer

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Abstract

Background: Coffee contains several bioactive compounds relevant to colon physiology. Although coffee intake is a proposed protective factor for colorectal cancer, current evidence remains inconclusive.

Methods: We investigated the association between coffee consumption and risk of colorectal cancer in 5,145 cases and 4,097 controls from the Molecular Epidemiology of Colorectal Cancer (MECC) study, a population-based case–control study in northern Israel. We also examined this association by type of coffee, by cancer site (colon and rectum), and by ethnic subgroup (Ashkenazi Jews, Sephardi Jews, and Arabs). Coffee data were collected by interview using a validated, semi-quantitative food frequency questionnaire.

Results: Coffee consumption was associated with 26% lower odds of developing colorectal cancer [OR (drinkers vs. nondrinkers), 0.74; 95% confidence interval (CI), 0.64–0.86; $P < 0.001$]. The inverse association was also observed for decaffeinated coffee consumption alone (OR, 0.82; 95% CI, 0.68–0.99; $P = 0.04$) and for boiled coffee (OR, 0.82; 95% CI, 0.71–0.94; $P = 0.004$). Increasing consumption of coffee was associated with lower odds of developing colorectal cancer. Compared with <1 serving/day, intake of 1 to <2 servings/day (OR, 0.78; 95% CI, 0.68–0.90; $P < 0.001$), 2 to 2.5 servings/day (OR, 0.59; 95% CI, 0.51–0.68; $P < 0.001$), and >2.5 servings/day (OR, 0.46; 95% CI, 0.39–0.54; $P < 0.001$) were associated with significantly lower odds of colorectal cancer ($P_{trend} < 0.001$), and the dose–response trend was statistically significant for both colon and rectal cancers.

Conclusions: Coffee consumption may be inversely associated with risk of colorectal cancer in a dose–response manner.

Impact: Global coffee consumption patterns suggest potential health benefits of the beverage for reducing the risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 25(4); 634–9. ©2016 AACR.*

Introduction

Coffee is one of the most widely consumed beverages in the world (1, 2). It contains many potentially bioactive components that are relevant to colon physiology, including polyphenols (mainly chlorogenic acids), melanoidins, diterpenes, and caffeine, among others (3, 4). Although the levels of these compounds vary by species of coffee bean, degree of roasting, brewing technique, and serving size, exposure to one or more of them may promote colon health via anti-mutagenic or antioxidant properties, reduction of bile acid secretion, modification of microbiome composition, and/or enhancement of critical bowel functions (e.g., motility, stool output; ref. 3). Based on the potential benefits of coffee's biochemical components, the beverage has been proposed as a protective agent for colorectal cancer, the third most common cancer in males and in females in the United States (5) and the fourth most common cause of cancer death worldwide (6).

Despite the biologic plausibility of coffee's chemopreventive properties, epidemiologic evidence of an association between coffee intake and the risk of colorectal cancer remains inconclusive. Existing evidence generally supports an inverse association, but results reported in the literature vary by study design (case–control vs. cohort), cancer site (colon vs. rectum), sex, and ethnicity (3, 7–18). The most recent meta-analysis considered 25 case–control studies and 16 cohort studies with over 25,000 cases (14). This meta-analysis observed suggestive evidence of an inverse association in cohort studies, whereas case–control studies showed that the highest category of coffee consumption was associated with a statistically significant 15% to 21% lower risk of colorectal cancer or colon cancer (not rectal cancer) as compared with the lowest category of consumption. Further, a growing body of evidence suggests coffee consumption as a protective factor for other gastrointestinal cancers (19–21). The goal of the current investigation was to examine the association between coffee intake and risk of colorectal cancer in a well-powered study with comprehensive data on clinical characteristics, including anatomic site, coffee preparation, and potential confounders.

Materials and Methods

Study description

The Molecular Epidemiology of Colorectal Cancer Study (MECC) is a population-based, incidence-density case–control study of pathologically confirmed incident colorectal cancer cases and their matched controls from a geographically defined area of

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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northern Israel (22). Subject recruitment began in 1998 and remains ongoing. Individually matched controls with no personal history of colorectal cancer are selected from the Clalit Health Services database to ensure representation of the same source population that gives rise to cases. Clalit Health Services is the largest health care provider in Israel, covering more than 70% of the study cases and providing a nationally standardized health services basket. Matching factors include year of birth, sex, primary clinic location, and ethnicity (Jewish vs. non-Jewish). Subjects are interviewed within 6 months of diagnosis to obtain demographic data, clinical information, family history, and dietary habits. The present analysis included 5,145 cases and 4,097 controls with high-quality food frequency questionnaire data, for a total of 9,242 MECC study participants (Table 1). Written informed consent was obtained at the time of enrollment according to Institutional Review Board-approved protocols at Carmel Medical Center (Haifa) and the University of Southern California.

Table 1. Demographic and clinical characteristics of MECC study participants ($N = 9,242$)

	Cases ($n = 5,145$) *N* (%)	Controls ($n = 4,097$) *N* (%)
Age, mean (SD)	68.7 (12.2)	70.7 (11.9)
Sex (%)		
Male	2,689 (52.3)	2,121 (51.8)
Female	2,456 (47.7)	1,976 (48.2)
Ethnicity (%)		
Ashkenazi	3,248 (63.1)	2,416 (59.0)
Sephardi	1,006 (19.5)	976 (23.8)
Arab	764 (14.8)	487 (11.9)
Non-Jewish, non-Arab	126 (2.4)	59 (1.4)
Family history of CRC (first-degree relative)	447 (8.7)	242 (5.9)
Vegetable consumption (≥5/day)	2,882 (56.0)	2,524 (61.6)
Sports activity	1,454 (28.3)	1,680 (41.0)
Statins use, 5+ years	690 (13.4)	772 (18.8)
Daily aspirin use, 2+ years	1,009 (19.6)	1,188 (29.0)
Smoking status		
Current	424 (8.2)	525 (12.8)
Former	1,487 (28.9)	1,173 (28.6)
Never	2,826 (54.9)	2,020 (49.3)
Site		
Colon	3,788 (73.6)	—
Rectum	1,160 (22.5)	—
Other or missing	197 (3.8)	—
Stage		
1	385 (7.5)	—
2	825 (16.0)	—
3	586 (11.4)	—
4	471 (9.2)	—
Missing[a]	2,862 (55.6)	—

Abbreviation: CRC, colorectal cancer.
[a]Although T and N staging was available for all cases, metastasis staging requires individual medical record review which is complete for only 2,267 cases. Medical record review continues.

Assessment of coffee consumption

Coffee intake data were collected by in-person interview using a validated, semi-quantitative food frequency questionnaire adapted to the Israeli population. The questionnaire assessed the frequency of consumption of decaffeinated coffee, boiled black coffee, black coffee (espresso), instant coffee, and filter coffee 1 year prior to diagnosis for cases or interview for controls. The questionnaire also assessed intake of tea and other beverages, allowing for the calculation of total liquid consumption. To assure high-quality data for analysis, 200 individuals with missing or extreme values for energy consumption (total caloric intake <600 or >4000) were excluded. Intake of each coffee type was calculated by converting a semiquantitative scale into servings per day, and total daily consumption was calculated by summing servings per day of decaffeinated, boiled, espresso, instant, and filter coffees. Further, 130 participants without complete data for all five coffee types and 24 outliers with total coffee consumption greater than four standard deviations from the mean were excluded. Finally, total coffee intake was converted into two derived variables: (i) drinkers (>0 servings/day) and non-drinkers (0 servings/day); and (ii) ordered categories of coffee drinking informed by quartiles of consumption in controls. These four categories consisted of <1 serving/day (reference category), ≥1 and <2 servings/day, ≥2 and ≤2.5 servings/day, and >2.5 servings/day.

Statistical analysis

The associations between total coffee consumption and established colorectal cancer–associated risk and protective factors were examined using χ^2 tests of independence and analysis of variance. The association between coffee and colorectal cancer was assessed using unconditional and conditional logistic regression, with adjustment for known colorectal cancer risk factors. The inclusion criteria for covariates were study matching factors (for unconditional analyses) and those with a statistically significant association with colorectal cancer identified in prior published analyses of the MECC data. The covariates included were age, sex, ethnicity (Jewish vs. non-Jewish), family history of colorectal cancer in a first-degree relative, vegetable consumption (≥5 servings/day vs. <5 servings/day), sports participation (yes vs. no), statin use (duration ≥5 years vs. <5 years), daily low-dose aspirin use (duration ≥2 years vs. <2 years), and smoking status (current/former/never). We conducted a test for trend based on an ordinal score corresponding to the four categories of daily coffee consumption described above. The associations were further explored with stratification by ethnic subgroup (Ashkenazi Jews, Sephardi Jews, and Arabs), cancer site (colon and rectum), and type of coffee (decaffeinated, boiled, espresso, instant, and filtered).

Results

The demographic and clinical characteristics of the study participants for analysis are summarized in Table 1. Findings reported here are based on analyses of 5,145 cases and 4,097 controls (with 3,574 matched pairs for conditional logistic regression). The majority of participants were of Ashkenazi Jewish descent (61.3%), with individuals of Sephardi Jewish (21.4%) and Arab (13.5%) descent comprising the other major ethnic subgroups. As compared with controls, on average, cases were slightly younger (matched for age within 1 year), were less likely to take statins or low dose aspirin, were less likely to be physically active, were less likely to consume 5 or more servings of vegetables per day, were less likely to smoke, and had a stronger family history of colorectal cancer. Overall, 74% of all incident cases in the source population were identified and approached, and 84% of these agreed to participate (case participation rate, 62%). Among population-based controls, the participation rate was 52%.

The mean total coffee intake among controls was 2.0 servings per day. Arabs had the highest total consumption with an average of 3.3 servings per day, followed by Sephardi Jews with a mean of 2.1 servings per day, and finally by Ashkenazi Jews with an average of 1.8 servings per day. Total coffee consumption in the complete sample, stratified by major ethnic group, can be visualized in Fig. 1. Mean coffee consumption was statistically significantly different across these 3 groups ($P < 0.001$). Instant coffee was the most common type consumed by Ashkenazi and Sephardi Jews, whereas boiled coffee was the most popular among Arabs (Supplementary Fig. S1). Total coffee consumption was associated with established colorectal cancer–associated factors: vegetable consumption ($P < 0.001$), daily low-dose aspirin use ($P = 0.03$), sports participation ($P < 0.001$), smoking status ($P < 0.001$), and sex ($P < 0.001$).

Table 2 summarizes the unconditional logistic regression results for coffee consumption and risk of cancer, comparing coffee drinkers to non-drinkers. The results from matched analyses of 3,574 pairs were not qualitatively different from those conducted using an unconditional approach, so we present unmatched analyses due to power considerations. Coffee consumption was associated with a 26% reduction in the odds of developing colorectal cancer after adjusting for study matching factors and other known risk-associated factors [OR (drinkers of any amount versus non-drinkers): 0.74; 95% confidence interval (CI): 0.64–0.86; $P < 0.001$]. Additional adjustment for total daily liquid consumption yielded a comparable overall colorectal cancer adjusted OR (0.80; 95% CI, 0.68–0.93; $P = 0.005$), indicating that liquid intake did not account for the observed association. Adjustment for total calorie consumption in addition to matching factors and known risk factors also yielded a comparable OR (0.74; 95% CI, 0.63–0.86; $P < 0.001$). Upon stratification by coffee type, an inverse association was maintained for those consuming decaffeinated coffee (overall colorectal cancer adjusted OR, 0.82; 95% CI, 0.68–0.99; $P = 0.04$) as well as boiled coffee (overall colorectal cancer adjusted OR, 0.82; 95% CI, 0.71–0.94; $P = 0.004$; Table 3).

Upon stratification by ethnic subgroup, the OR estimates for Ashkenazi Jews, Sephardi Jews, and Arabs were consistent with the total sample. Results were statistically significant for only Ashkenazi Jews and Sephardi Jews, the two largest ethnic subgroups represented in the MECC study (Table 2). When considering colon and rectal cancers separately, the OR estimates show an inverse association between coffee consumption and risk of cancer in either tumor location. The colon cancer estimates were highly statistically significant in the total sample and in Sephardi Jews. In the total MECC sample, the association for rectal cancer was attenuated as compared with that for colon cancer but reached statistical significance at the $P < 0.05$ level (OR, 0.78; 95% CI, 0.61–0.99; $P = 0.04$). In addition, we did not observe evidence of meaningful effect modification of the association of coffee consumption and risk of colorectal cancer by other covariates, including sex, vegetable consumption, physical activity, statins, aspirin, smoking, or family history, with the exception of age ($OR_{interaction} = 1.01$; 95% CI, 1.00–1.03; $P = 0.04$).

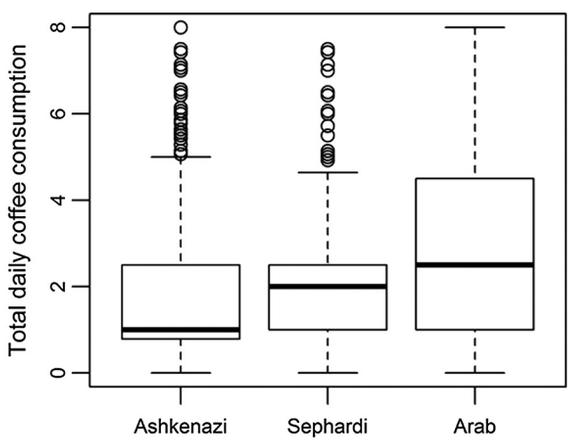

Figure 1.
Total daily coffee consumption (servings/day) by major ethnic subgroup in the MECC study.

Table 4 summarizes logistic regression results when considering daily total coffee intake in four categories. Compared with drinkers of <1 serving/day, drinkers of 1 to <2 servings/day (OR, 0.78; 95% CI, 0.68–0.90; $P < 0.001$), 2 to 2.5 servings/day (OR, 0.59; 95% CI, 0.51–0.68; $P < 0.001$), and >2.5 servings/day (OR, 0.46; 95% CI, 0.39–0.54; $P < 0.001$) had statistically significant lower odds of developing colorectal cancer in the total MECC sample. Notably, we observed an inverse dose–response relation between coffee intake and the odds of developing colorectal cancer ($P_{trend} < 0.001$). When colon and rectal cancers were examined individually, the direction and magnitude of ORs for all non-reference categories remained essentially unchanged from colorectal cancer estimates and were highly statistically significant. Table 4 also details the same set of analyses stratified by ethnic subgroup. The statistically significant inverse dose–response relation between coffee and risk of colorectal cancer, colon, or rectal cancers held in the two largest ethnic subgroups (Ashkenazi and Sephardi Jews). Although power was limited for the analysis of Arab participants, consistent directions of OR point estimates were observed.

Discussion

Here, we demonstrate that modest coffee consumption (≥1 and <2 servings/day) is associated with a meaningful reduction in the odds of developing colorectal cancer in a large, population-based case–control study, and that the highest category of consumption (>2.5 servings/day) is associated with a 54% reduction in the odds of developing disease. The inverse association was consistent for decaffeinated and boiled coffees, colon and rectal cancers, and observed among all ethnic subgroups in our study. Evidence of a dose–response relation with greater risk reduction associated with increasing consumption supports the biologic plausibility of these findings.

The results from this study support the growing body of evidence suggesting coffee consumption as a protective factor for colorectal cancer (11, 15, 23) and as a predictor of reduced colorectal cancer recurrence and death (24). However, there are differences in results and interpretations of case–control and cohort studies (14, 18), possibly due to the different time period of exposure considered relative to cancer diagnosis. A subgroup analysis of cohort studies showed that studies with less than 10 years of follow-up were more likely to report an inverse association between coffee consumption and risk of colorectal cancer than those with follow-up longer than 10 years (15). With respect to dose, our finding of a statistically significant inverse association

Table 2. Association between coffee consumption and risk of colorectal cancer, colon cancer, and rectal cancer in all MECC participants and in major ethnic subgroups

	CRC (unadjusted)						CRC (adjusted[a])				Colon (adjusted[a])				Rectal (adjusted[a])			
	N_{case}	$N_{control}$	OR	95% LCL	95% UCL	*P*	OR	95% LCL	95% UCL	*P*	OR	95% LCL	95% UCL	*P*	OR	95% LCL	95% UCL	*P*
All coffee																		
Total MECC	5,146	4,097	0.73	0.64	0.82	<0.001	0.74	0.64	0.86	<0.001	0.74	0.63	0.87	<0.001	0.78	0.61	0.99	0.04
Ashkenazi	3,249	2,416	0.75	0.64	0.87	<0.001	0.82	0.68	0.98	0.03	0.83	0.69	1.01	0.06	0.81	0.61	1.09	0.17
Sephardi	1,006	976	0.66	0.49	0.87	0.004	0.59	0.42	0.83	0.003	0.57	0.40	0.82	0.002	0.75	0.43	1.32	0.32
Arab	764	487	0.66	0.39	1.11	0.12	0.72	0.37	1.40	0.33	0.75	0.37	1.53	0.43	0.59	0.24	1.43	0.24
Decaf coffee																		
Total MECC	5,146	4,097	0.70	0.60	0.81	<0.001	0.82	0.68	0.99	0.04	0.83	0.67	1.02	0.07	0.86	0.62	1.19	0.36
Ashkenazi	3,249	2,416	0.69	0.58	0.81	<0.001	0.84	0.67	1.04	0.11	0.87	0.69	1.10	0.23	0.80	0.55	1.16	0.23
Sephardi	1,006	976	0.82	0.57	1.20	0.31	0.67	0.42	1.08	0.10	0.60	0.35	1.03	0.06	0.98	0.47	2.04	0.95
Arab	764	487	0.36	0.11	1.24	0.11	0.44	0.12	1.59	0.21	0.32	0.06	1.64	0.17	1.17	0.20	6.79	0.74

NOTE: Odds ratios represent the relative odds associated with developing CRC for coffee-drinkers of any amount versus non-drinkers.
Abbreviations: CRC, colorectal cancer; LCL, lower confidence limit; UCL, upper confidence limit.
[a]Adjusted for sex, age, ethnic subgroup (total MECC only), vegetable consumption, sports participation, statin use, daily low-dose aspirin use, smoking status, and family history in a first-degree relative.

was observed at lower levels of coffee intake than some previous publications. For example, a recent dose–response analysis observed a statistically significant inverse relation associated with ≥4 cups/day (12), and another study in a Japanese population showed a U-shaped relation between coffee and colorectal cancer with decreased risk for up to 3 cups/day (25). In contrast to several earlier reports observing no statistically significant association for rectal cancer, our study demonstrated an inverse trend for both colon and rectal cancers (11, 12, 14). This difference is possibly due in part to a lack of power in prior studies.

A variety of potentially bioactive compounds in coffee could independently or in combination exert chemopreventive properties, and thus, several mechanisms of action have been proposed. Coffee constituents could influence colon health via roles in motility and fecal output, microbiome composition, inflammation, secretion of bile acids, insulin sensitivity, and the oxidative environment of the colon (26). With respect to specific components, chlorogenic acids are powerful antioxidants *in vitro* and are believed to modify expression of genes encoding phase II metabolism enzymes as well as to inhibit DNA methyltransferase (27). Polyphenols are hypothesized to exert antioxidant and antiproliferative effects as well as to induce cell-cycle arrest based on experimental evidence in colorectal cancer cell lines (28). The roasting products, melanoidins, may act *in vivo* as dietary fiber and could increase colon motility (27). The diterpenes cafestol and kahweol are plentiful in boiled and unfiltered coffees and may exert anticarcinogenic activity by enhancing defense systems against oxidative damage (7, 27, 29). Our finding of an inverse association for boiled coffee provides epidemiologic evidence in support of the protective role of these biochemical components. Caffeine may have antioxidant capacity (27), and it may limit the growth potential of human colon cancer cells (30). Our observation that an inverse association was present for decaffeinated coffee alone indicates that caffeine is unlikely to be the sole compound underlying coffee's protective properties.

Levels of exposure to these different compounds vary based on the type of coffee bean, roasting degree, brewing technique, and serving size. For example, cafestol and kahweol are removed by filtration, and thus, filter and instant coffee contain very little (4, 31). Further, more melanoidins are present in darker roasted coffees and those with higher powder/water ratio during the brewing process (26). Serving size has been shown to be the most important factor for intake of chlorogenic acids and melanoidins (3, 32). The lack of detailed information collected by most food frequency questionnaires makes it difficult to discern in an observational setting which coffee components are important. Few population-scale studies have focused on dietary intake of specific potentially bioactive components. However, one recent Japanese study demonstrated a decreased risk of colorectal cancer associated with coffee polyphenol intake (25). Relevant to our study, it is possible that differences in the strength of association between coffee consumption and colorectal cancer across ethnic subgroups could be driven in part by the different distribution of coffee types and serving sizes consumed.

Our study has several strengths as compared with prior investigations of the role of coffee-drinking and risk of developing colorectal cancer. Two major benefits include exceptional power to allow for stratified analyses and detailed questionnaire data to enable the analysis of different coffee types. We also evaluated caffeine status and indirectly investigated brewing methods of

Table 3. Association between boiled, espresso, instant, and filter coffee types and risk of colorectal cancer, colon cancer, and rectal cancer in all MECC participants

	CRC (unadjusted)				CRC (adjusted[a])				Colon (adjusted[a])				Rectal (adjusted[a])			
	OR	95% LCL	95% UCL	*P*	OR	95% LCL	95% UCL	*P*	OR	95% LCL	95% UCL	*P*	OR	95% LCL	95% UCL	*P*
Boiled	0.95	0.86	1.04	0.29	0.82	0.71	0.94	0.004	0.79	0.68	0.92	0.002	0.88	0.70	1.09	0.23
Espresso	0.85	0.76	0.95	0.005	0.89	0.77	1.03	0.11	0.88	0.76	1.03	0.11	0.90	0.72	1.12	0.35
Instant	1.03	0.95	1.12	0.44	1.07	0.96	1.19	0.21	1.09	0.97	1.21	0.16	1.08	0.91	1.28	0.36
Filter	1.12	0.90	1.38	0.31	1.11	0.86	1.43	0.43	1.19	0.90	1.56	0.22	0.89	0.58	1.37	0.60

NOTE: Odds ratios represent the relative odds associated with developing CRC for coffee-drinkers of any amount versus non-drinkers.
Abbreviations: CRC, colorectal cancer; LCL, lower confidence limit; UCL, upper confidence limit.
[a]Adjusted for sex, age, ethnicity, vegetable consumption, sports participation, statin use, daily low-dose aspirin use, smoking status, and family history in a first-degree relative.

Table 4. Association between coffee and cancer in all MECC subjects and in major ethnic subgroups from multivariable logistic regression

	CRC (unadjusted)						CRC (adjusted[a])[b]				Colon (adjusted[a])				Rectum (adjusted[a])			
Servings/day	N_{case}	$N_{control}$	**OR**	**95% LCL**	**95% UCL**	***P***	**OR**	**95% LCL**	**95% UCL**	***P***	**OR**	**95% LCL**	**95% UCL**	***P***	**OR**	**95% LCL**	**95% UCL**	***P***
Total MECC																		
<1	1,395	751	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—
≥1 and <2	1,651	1,235	0.72	0.64	0.81	<0.001	0.78	0.68	0.90	<0.001	0.79	0.68	0.92	0.002	0.78	0.63	0.97	0.02
≥2 and ≤2.5	1,274	1,221	0.56	0.50	0.63	<0.001	0.59	0.51	0.68	<0.001	0.57	0.49	0.66	<0.001	0.54	0.43	0.68	<0.001
>2.5	825	890	0.50	0.44	0.57	<0.001	0.46	0.39	0.54	<0.001	0.39	0.33	0.47	<0.001	0.50	0.40	0.64	<0.001
Ashkenazi																		
<1	987	506	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—
≥1 and <2	1,158	785	0.75	0.66	0.87	<0.001	0.82	0.69	0.97	0.02	0.84	0.70	1.00	0.06	0.75	0.57	0.97	0.03
≥2 and ≤2.5	789	745	0.54	0.47	0.63	<0.001	0.59	0.50	0.71	<0.001	0.61	0.50	0.74	<0.001	0.51	0.38	0.68	<0.001
>2.5	314	380	0.42	0.35	0.51	<0.001	0.44	0.35	0.56	<0.001	0.44	0.34	0.56	<0.001	0.45	0.32	0.65	<0.001
Sephardi																		
<1	230	135	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—
≥1 and <2	327	295	0.65	0.50	0.85	0.001	0.67	0.49	0.92	0.01	0.62	0.44	0.87	0.005	1.01	0.60	1.71	0.96
≥2 and ≤2.5	284	305	0.55	0.42	0.71	<0.001	0.56	0.41	0.77	<0.001	0.51	0.36	0.72	<0.001	0.81	0.48	1.38	0.45
>2.5	165	241	0.40	0.30	0.54	<0.001	0.37	0.26	0.53	<0.001	0.35	0.24	0.51	<0.001	0.52	0.29	0.92	0.03
Arab																		
<1	116	60	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—
≥1 and <2	121	73	0.86	0.56	1.31	0.48	0.98	0.60	1.59	0.92	1.04	0.61	1.78	0.87	0.80	0.40	1.61	0.54
≥2 and ≤2.5	186	118	0.82	0.55	1.20	0.30	0.96	0.61	1.49	0.84	0.99	0.61	1.61	0.98	0.89	0.48	1.63	0.70
>2.5	341	236	0.75	0.53	1.06	0.11	0.87	0.58	1.32	0.52	0.82	0.52	1.28	0.38	0.95	0.55	1.63	0.86

Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.

[a]Adjusted for sex, age, ethnicity, vegetable consumption, sports participation, statin use, daily low-dose aspirin use, smoking status, and family history in a first-degree relative.

[b]Adjusted CRC $P_{trend} < 0.001$ in all MECC participants, Ashkenazi Jews, and Sephardi Jews. Adjusted CRC $P_{trend} = 0.45$ in Arabs.

decoction (for boiled coffee) and gravitation (for filter coffee), which most prior studies have not been able to accomplish. Despite these strengths, our study was limited by a number of factors. Unlike prospective cohort study designs, data were collected for our case–control study at one point in time regarding usual coffee consumption 1 year prior to diagnosis and, thus, we could not assess duration of exposure. Further, no standardized measurements for serving size were available. Limitations of the observational nature of case–control designs, including the use of food frequency recall, also need to be considered in the interpretation of these results. Notably, we observed consistent results upon stratification by stage at diagnosis, alleviating concerns that recall bias may be more severe for patients with more advanced disease. Alternative explanations for an inverse association between coffee consumption and colorectal cancer include reverse causation, with digestive tract disease and bowel symptoms leading cases to avoid drinking coffee (14), and the possibility that total fluid consumption or hot beverage drinking may reduce risk of colorectal cancer through a mechanism of increased colon motility. However, we observed that controlling for total beverage consumption did not attenuate the inverse relation between coffee and colorectal cancer. All case–control studies are potentially vulnerable to residual confounding, including ours, and it is possible that measured or unmeasured risk factors might lead to biased estimates of the association between coffee consumption and risk of colorectal cancer.

In conclusion, this large case–control study provides evidence of an inverse, dose–response association between coffee drinking and the odds of colorectal cancer, colon, and rectal cancer incidence. It also suggests that caffeine is not the critical component responsible for this inverse association and that the protective association was not observed for filtered or instant coffees. The health risks of coffee consumption are low, but additional evidence is warranted before advocating for coffee consumption as a nutraceutical approach to reduce the risk of colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.L. Schmit, G. Rennert, S.B. Gruber
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.S. Rennert, G. Rennert, S.B. Gruber
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.L. Schmit, H.S. Rennert, G. Rennert, S.B. Gruber
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