Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study[1–4]

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ABSTRACT

Background: Coffee and tea are widely consumed globally and are rich sources of potential chemopreventive compounds. Epidemiologic data for coffee and tea intakes in relation to colorectal cancer remain unclear. Despite differences in gut physiology, few studies have conducted investigations by anatomic subsites.

Objective: We evaluated coffee and tea intakes (caffeinated and decaffeinated) in relation to colon (proximal and distal) and rectal cancers.

Design: The NIH-AARP Diet and Health Study included 489,706 men and women who completed a baseline (1995–1996) self-administered questionnaire of demographics, diet, and lifestyle. Over a median of 10.5 y of follow-up, we identified 2863 proximal colon, 1993 distal colon, and 1874 rectal cancers. Multivariable HRs and 95% CIs were estimated by using Cox regression.

Results: Approximately 16% of participants drank ≥4 cups coffee/d. Compared with nondrinkers, drinkers of 4–5 cups coffee/d (HR: 0.85; 95% CI: 0.75, 0.96) and ≥6 cups coffee/d (HR: 0.74; 95% CI: 0.61, 0.89; *P*-trend < 0.001) had a lower risk of colon cancer, particularly of proximal tumors (HR for ≥6 cups/d: 0.62; 95% CI: 0.49, 0.81; *P*-trend < 0.0001). Results were similar to those overall for drinkers of predominantly caffeinated coffee. Although individual HRs were not significant, there was a significant *P*-trend for both colon and rectal cancers for people who drank predominantly decaffeinated coffee. No associations were observed for tea.

Conclusions: In this large US cohort, coffee was inversely associated with colon cancer, particularly proximal tumors. Additional investigations of coffee intake and its components in the prevention of colorectal cancer by subsites are warranted. The NIH-AARP Diet and Health Study was registered at clinicaltrials.gov as NCT00340015. *Am J Clin Nutr* 2012;96:374–81.

INTRODUCTION

Coffee and tea are widely consumed globally, and their potential role in the cause of chronic disease has attracted considerable attention (1–6). Although tea is the most popular beverage after water in certain areas of the world, relatively low amounts are consumed in the United States (1 lb per capita per year in 2009) in comparison with coffee (7 lb per capita per year in 2009) (7). Bioactive compounds in tea, particularly green tea polyphenols, have shown some promising results in cancer-prevention trials, but epidemiologic studies have not yielded supportive results (8). Coffee contains numerous bioactive compounds that may modulate cancer risk, including diterpenes, cafestol, kahweal, polyphenols, chlorogenic acid, and caffeic acid (9–12).

The relation between coffee drinking and colorectal cancer has been investigated in previous epidemiologic studies with ambiguous results (12). Previous meta-analyses of case-control and cohort studies yielded promising evidence that suggested an inverse relation between coffee drinking and colorectal cancer (13–15), whereas null findings were recently reported in a pooled analysis of 13 prospective studies (16).

However, few studies have addressed the potential variation in the relation between coffee and tea intakes and colorectal cancer by anatomic subsites within the gut. Evidence from epidemiologic studies, which suggested that key risk factors for colorectal cancer (eg, adult height, aspirin use, physical activity, and meat components) may differ substantially by subsites (17–22), provided additional support for the investigation of the following 3 separate endpoints: the proximal colon, distal colon, and rectum (23).

We evaluated the association between the intake of coffee and tea in relation to risk of colorectal cancer by anatomic subsite (ie, proximal colon, distal colon, and rectum) in a large prospective cohort. In addition, we examined the association for the intake of caffeinated compared with decaffeinated coffee and tea and conducted stratified analyses according to a number of colorectal cancer risk factors.

SUBJECTS AND METHODS

Study population

The NIH-AARP Diet and Health Study (www.clinicaltrials.gov; NCT00340015) has been described previously (24). Be-

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tween 1995 and 1996, 617,119 AARP members, who were aged 50–71 y and resided in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI), completed a baseline questionnaire. Of the 566,401 participants who satisfactorily completed the baseline questionnaire, we excluded proxy respondents (n = 15,760) and participants with prevalent cancer (according to cancer registries or self-report; n = 51,223) or self-reported end-stage renal disease (n = 997) at baseline, a death-only report for any cancer (n = 1804), zero person-years of follow-up (n = 36), an implausible total energy intake (n = 4188), or a missing response for coffee consumption (n = 2687), which resulted in an analytic cohort of 489,706 participants.

Exposure assessment

Study participants completed a self-administered questionnaire that included sections on demographics, diet, anthropometric measurements, and lifestyles (eg, exogenous hormone use, family history of cancer, physical activity, medical conditions, reproductive factors, and smoking) and a 124-item food-frequency questionnaire [ie, the National Cancer Institute's Diet History Questionnaire (24)], with information on the frequency of intake and portion sizes over the past year. More specifically, coffee and tea intakes over the past 12 mo was assessed by using 10 categories that ranged from none to ≥6 cups/d. Participants were dichotomized by using their response to whether their coffee or tea was caffeinated or decaffeinated more than one-half of the time. In a validation set of 1953 participants who also completed 2 nonconsecutive 24-h dietary recalls, Spearman's correlations between 24-h dietary recalls and the food-frequency questionnaire were 0.80 for coffee, 0.64 for caffeinated coffee, and 0.48 for decaffeinated coffee (25). In this subset of NIH-AARP Study participants who completed two 24-h dietary recalls, 80% of subjects drank ground coffee, 18% of subjects drank instant coffee, and 1% of subjects drank espresso coffee. Within 6 mo after the baseline questionnaire was returned, a second questionnaire was administered (response rate: 62%) in which we collected information on colorectal cancer screening, nonsteroidal antiinflammatory drug use, and other variables.

Case ascertainment

Cancer cases were identified through linkage with state cancer registries in the 8 original states plus Texas and Arizona, areas to which participants most commonly moved during follow-up. Follow-up began on the date of questionnaire return and continued until the cancer diagnosis, movement out of the cancer registry area, loss to follow-up, death, or 31 December 2006, whichever came first. Colorectal cancers were defined by anatomic sites and histology codes as defined by the third edition of the International Classification of Diseases for Oncology (26) and included codes C180–C189, C199, C209, and C260. Colorectal subsites were further classified as proximal colon (C180–C184), distal colon (C185–C187), and rectum (C199 and C209) (20). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Statistics

We estimated HRs and 95% CIs by using Cox proportional hazards regression models adjusted for established colorectal cancer risk factors with person-years as the underlying time metric. We modeled 6 categories of coffee intake (none, <1 cup/wk, and 1, 2–3, 4–5, and ≥6 cups/d) and 5 categories of tea intake (none, <1 cup/mo, 1–3 cups/mo, 1–6 cups/wk, and ≥1 cups/d) with the lowest category [0 cups (none)] as the referent group. Missing values were included in the multivariate model as dummy variables. P values for linear trends were calculated by using median values within quintiles. The proportional hazards assumption was verified with a time-interaction model by using the following 3 categories: baseline to <3 y, 3–6 y, and >6 y of follow-up. We also conducted a lag analysis that excluded the first 2 y of follow-up and evaluated potential interactions by sex, smoking status, diabetes, physical activity, BMI, red-meat consumption, stage of cancer, alcohol intake, and menopausal hormone use in women with inclusion of cross-product terms in the models. Dietary variables in models were energy-adjusted by using the nutrient-density method (27). All statistical tests were 2-sided and considered statistically significant at $P < 0.05$; analyses were conducted with SAS software (version 9.1.3; SAS Institute).

RESULTS

During a median follow-up of 10.5 y (4,454,656 person-years), we identified 6946 incident colorectal cancers (5072 colon and 1874 rectal cancers). We observed a higher proportion of proximal colon cancers (n = 2863) than distal colon cancers (n = 1,993), and 216 colon cancers had an unknown subsite location. Approximately 90% of the cohort drank coffee, and 16% of the cohort drank ≥4 cups coffee/d. Compared with nondrinkers, heavy coffee drinkers (≥6 cups/d) were more likely to be men, current smokers, and physically inactive and consumed more red meat and alcohol but less fruit and vegetables (**Table 1**). The majority of heavy coffee drinkers reported consuming predominantly caffeinated coffee.

As shown in **Table 2**, there was an inverse association between individuals who drank 4–5 cups coffee/d compared with nondrinkers with colon cancer (HR: 0.85; 95% CI: 0.75, 0.96), and the association was even stronger for subjects who drank ≥6 cups coffee/d (HR: 0.74; 95% CI: 0.61, 0.89); the P-trend across categories was <0.001. By anatomic subsites, the consumption of ≥6 cups coffee/d was associated with a strong inverse association for proximal colon cancer (HR: 0.62; 95% CI: 0.48, 0.81; P-trend <0.001); however, no association was observed for distal colon cancer (HR: 0.86; 95% CI: 0.64, 1.14; P-trend = 0.400) or rectal cancer (HR: 1.01; 95% CI: 0.76, 1.34; P-trend = 0.400).

Individuals who consumed 4–5 or ≥6 cups caffeinated coffee/d compared with none had a decreased risk of colon cancer [HRs of 0.86 (95% CI: 0.75, 0.98) and 0.74 (95% CI: 0.60, 0.91), respectively; P-trend < 0.001). Similarly, a protective association was also observed for decaffeinated coffee and colon cancer [HR for 4–5 cups coffee/d: 0.81 (95% CI: 0.67, 0.99); HR for ≥6 cups/d: 0.73 (95% CI: 0.50, 1.07); P-trend = 0.005]. By subsites, an analogous inverse association was shown between the highest intake, relative to nondrinkers, of caffeinated (HR: 0.59; 95% CI: 0.44, 0.79; P-trend < 0.001) and decaffeinated coffee (HR: 0.68; 95% CI: 0.40, 1.14; P-trend = 0.005) and proximal colon cancer. There was also a significant linear trend observed between individuals who

TABLE 1
Selected characteristics of the NIH-AARP Diet and Health Study by category of coffee intake in 489,706 participants (292,211 men and 197,495 women)

Characteristic	None	≤1 cup/wk	1 cup/d	2–3 cups/d	4–5 cups/d	≥6 cups/d
Participants (*n*)	49,996	80,670	81,080	200,716	59,055	18,189
Caffeinated coffee (%)	—	41.4	58.2	68.8	74.6	78.6
Decaffeinated coffee (%)	—	50.5	38.4	28.1	22.2	18.2
Tea (%)	62.0	77.6	71.6	70.8	66.8	59.2
Men (%)	52.2	56.6	44.7	61.6	67.0	68.4
Age (y)	61.3 ± 0.02[1]	61.9 ± 0.02	62.8 ± 0.02	62.2 ± 0.01	61.4 ± 0.02	60.8 ± 0.04
Non-Hispanic white (%)	89.1	85.8	88.2	93.7	95.7	96.1
Family history of colorectal cancer (%)	8.8	8.6	8.8	8.7	8.8	8.3
Currently married (%)	64.6	64.2	67.9	70.8	71.5	68.7
Education, college graduate (%)	41.7	41.1	37.6	38.3	37.5	31.5
BMI (kg/m^2)	27.3 ± 0.03	27.3 ± 0.02	27.1 ± 0.02	27.0 ± 0.01	27.0 ± 0.02	27.0 ± 0.04
Diabetes (%)	9.5	10.0	9.7	8.4	8.1	8.1
Current smoker (%)	6.1	6.1	7.0	12.2	22.6	36.9
Alcohol [>3 drinks/d (%)]	4.1	5.8	6.5	8.8	9.6	8.8
Vigorous physical activity ≥5 times/wk (%)	21.5	19.2	19.2	18.9	18.5	18.8
Colorectal screening (%)[2,3]	42.6	46.0	45.1	45.1	42.9	39.8
Ever used menopausal hormone therapy (%)[4]	51.4	53.9	53.6	54.5	50.7	44.8
Total energy (kcal/d)	1790 ± 3.6	1746 ± 2.8	1767 ± 2.7	1839 ± 1.7	1985 ± 3.5	2175 ± 7.1
Fruit (servings/1000 kcal)	1.96 ± 0.006	1.96 ± 0.004	1.86 ± 0.004	1.62 ± 0.002	1.41 ± 0.004	1.24 ± 0.008
Vegetables (servings/1000 kcal)	2.31 ± 0.006	2.33 ± 0.004	2.26 ± 0.004	2.20 ± 0.002	2.12 ± 0.004	2.00 ± 0.008
Red meat (g/1000 kcal)	32.6 ± 0.12	31.9 ± 0.08	33.2 ± 0.07	35.3 ± 0.05	37.7 ± 0.09	40.0 ± 0.18
Dietary calcium intake (mg/1000 kcal)	439 ± 0.91	440 ± 0.68	429 ± 0.64	428 ± 0.39	426 ± 0.71	424 ± 1.33
Regular nonsteroidal antiinflammatory drug use (%)[3,5]	60.0	64.19	66.5	68.9	69.5	68.5

[1] Mean ± SD (all such values).
[2] Screening by endoscopy only.
[3] Response from second questionnaire.
[4] Women only.
[5] Defined as ≥2 times/mo.

drank decaffeinated coffee and rectal cancer (HR for ≥6 cups/d: 0.77; 95% CI: 0.40, 1.46; *P*-trend = 0.003) and a tendency toward a lower risk of distal colon cancer (HR for ≥ 6 cups/d: 0.77; 95% CI: 0.42, 1.42; *P*-trend = 0.090); however, CIs were large because of small case numbers in the highest category of coffee intake (11 cases for distal colon and 10 cases for rectal cancers). The exclusion of cases diagnosed during the first 2 y of follow-up did not alter associations. However, the beneficial effect of coffee intake on colon cancer was confined to the first 6 y of follow-up and was attenuated in the latter 4 y when consumption of ≥6 cups coffee/d was compared to none (for events in the first 3 y, HR: 0.72; 95% CI: 0.50, 1.03; *P*-trend = 0.007; for years 3–6, HR: 0.56; 95% CI: 0.38, 0.81; *P*-trend < 0.001; and for years 6–10: HR: 0.87; 95% CI: 0.67, 1.14; *P*-trend = 0.820; data not shown).

The intake of tea was not associated with colon or rectal cancer (for ≥1cup/d, HR: 0.99; 95% CI: 0.91, 1.08; *P*-trend = 0.500; for none, HR: 0.92; 95% CI: 0.80, 1.07; *P*-trend = 0.800; **Table 3**). By subsites, there was a modest inverse association for the consumption of ≥1 cup decaffeinated tea/d relative to not drinking any tea with proximal colon cancer (HR: 0.81; 95% CI: 0.67, 0.98; *P*-trend = 0.060), but a positive association was observed with distal colon cancer (HR: 1.24; 95% CI: 1.01, 1.52; *P*-trend = 0.050).

Stratified analyses across a number of colorectal cancer risk factors revealed consistent associations with coffee. Results for selected variables (ie, sex, smoking, diabetes, BMI, and red-meat consumption) are presented in **Table 4**. Residual confounding by smoking was a potential concern because smoking is a positive risk factor for colon cancer (28–30), and heavy coffee drinkers were more likely to be current smokers. The coffee association appeared to be the weakest in never smokers, although the HR for the highest intake of coffee was in the same direction and of similar magnitude (0.61, 95% CI: 0.35, 1.04, *P*-trend = 0.4) as the association in former and current smokers, although the *P*-trend was not significant. However, we also noted that the *P*-interaction by smoking status was not significant ($P = 0.5$), and as such these differences may have been due to chance.

DISCUSSION

In our study, we showed that caffeinated and decaffeinated coffee drinkers had a decreased risk of colon cancer, whereas decaffeinated coffee drinkers also had a lower risk of rectal cancer. The inverse association for colon cancer was primarily in tumors of the proximal colon with no significant associations observed for the distal colon. The inverse association between coffee intake and colon cancer remained consistent in stratified analyses across a variety of colorectal risk factors but was somewhat attenuated in the latter years of follow-up. No associations were observed for tea.

In general, results from individual prospective cohort studies for coffee with colorectal cancer have been ambiguous (31–37). Meta-analyses of case-control and cohort studies (13–15) have shown results that were comparable to our findings, although a recent pooled analysis of 13 prospective studies (16) showed no significant association. Explanations for differences between the current findings and the pooling-project results are unclear but may include the use of a standard questionnaire in a single

TABLE 2
HRs for colorectal cancer by coffee intake in the NIH-AARP Diet and Health Study[1]

	All coffee		Caffeinated coffee		Decaffeinated coffee	
Outcome	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Colorectal	6946	—	6946	—	6946	—
None	647	1.00	2906	1.00	4955	1.00
<1 cup/wk	1083	0.97 (0.88, 1.07)	463	0.97 (0.86, 1.10)	531	0.96 (0.86, 1.08)
1 cup/d	1206	1.00 (0.90, 1.10)	699	0.99 (0.89, 1.11)	468	1.01 (0.90, 1.14)
2–3 cups/d	2999	0.98 (0.90, 1.07)	2099	1.01 (0.92, 1.10)	795	0.93 (0.84, 1.03)
4–5 cups/d	785	0.87 (0.78, 0.97)	597	0.90 (0.80, 1.00)	159	0.79 (0.66, 0.94)
≥6 cups/d	226	0.80 (0.69, 0.94)	182	0.83 (0.70, 0.99)	38	0.74 (0.53, 1.02)
P-trend	—	0.001	—	0.008	—	<0.001
Colon	5072	—	5072	—	5072	—
None	491	1.00	2198	1.00	3552	1.00
<1 cup/wk	795	0.94 (0.84, 1.05)	319	0.89 (0.77, 1.03)	414	0.99 (0.87, 1.13)
1 cup/d	887	0.97 (0.87, 1.08)	506	0.95 (0.84, 1.08)	358	1.02 (0.89, 1.17)
2–3 cups/d	2177	0.95 (0.86, 1.06)	1503	0.96 (0.87, 1.07)	597	0.93 (0.82, 1.05)
4–5 cups/d	570	0.85 (0.75, 0.96)	427	0.86 (0.75, 0.98)	123	0.81 (0.67, 0.99)
≥6 cups/d	152	0.74 (0.61, 0.89)	119	0.74 (0.60, 0.91)	28	0.73 (0.50, 1.07)
P-trend	—	<0.001	—	<0.001	—	0.005
Proximal colon	2863	—	2863	—	2863	—
None	292	1.00	1281	1.00	1982	1.00
<1 cup/wk	473	0.94 (0.81, 1.09)	179	0.86 (0.71, 1.04)	258	1.02 (0.86, 1.21)
1 cup/d	511	0.94 (0.81, 1.09)	289	0.92 (0.78, 1.09)	207	0.98 (0.82, 1.18)
2–3 cups/d	1202	0.90 (0.79, 1.02)	835	0.91 (0.80, 1.05)	327	0.86 (0.73, 1.00)
4–5 cups/d	312	0.80 (0.68, 0.95)	225	0.79 (0.66, 0.94)	74	0.83 (0.64, 1.08)
≥6 cups/d	73	0.62 (0.48, 0.81)	54	0.59 (0.44, 0.79)	15	0.68 (0.40, 1.14)
P-trend	—	<0.001	—	<0.001	—	0.005
Distal colon	1993	—	1993	—	1993	—
None	180	1.00	813	1.00	1427	1.00
<1 cup/wk	290	0.93 (0.77, 1.12)	129	0.96 (0.76, 1.20)	139	0.92 (0.74, 1.15)
1 cup/d	342	1.02 (0.85, 1.23)	195	1.00 (0.81, 1.22)	139	1.10 (0.88, 1.38)
2–3 cups/d	884	1.05 (0.89, 1.24)	614	1.06 (0.90, 1.26)	239	1.02 (0.84, 1.24)
4–5 cups/d	230	0.92 (0.75, 1.12)	187	1.01 (0.82, 1.24)	38	0.68 (0.48, 0.97)
≥6 cups/d	67	0.86 (0.64, 1.14)	55	0.90 (0.66, 1.23)	11	0.77 (0.42, 1.42)
P-trend	—	0.400	—	0.700	—	0.090
Rectal	1874	—	1874	—	1874	—
None	156	1.00	708	1.00	1403	1.00
<1 cup/wk	288	1.06 (0.87, 1.29)	144	1.22 (0.98, 1.54)	117	0.88 (0.70, 1.13)
1 cup/d	319	1.08 (0.89, 1.31)	193	1.12 (0.91, 1.39)	110	0.98 (0.77, 1.26)
2–3 cups/d	822	1.08 (0.91, 1.29)	596	1.14 (0.96, 1.37)	198	0.94 (0.76, 1.16)
4–5 cups/d	215	0.94 (0.76, 1.16)	170	1.00 (0.80, 1.25)	36	0.71 (0.50, 1.03)
≥6 cups/d	74	1.01 (0.76, 1.34)	63	1.11 (0.82, 1.50)	10	0.77 (0.40, 1.46)
P-trend	—	0.400	—	0.800	—	0.003

[1] HRs and 95% CIs were estimated by using Cox proportional hazards regression models with person-years as the underlying time metric adjusted for age (continuous), sex, race (non-Hispanic white, non-Hispanic black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown), education (<11 y or unknown, high school graduate, some college, or college graduate), smoking status (never, former, or current), time since quitting for former smokers, smoking dose, ever smoke a pipe or cigar, diabetes (yes or no), colorectal screening (yes or no), family history of colorectal cancer (yes or no), regular nonsteroidal antiinflammatory drug use (yes or no), marital status (married: yes or no), BMI (in kg/m^2; <18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35), frequency of vigorous physical activity (never or rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), calories (continuous), fruit and vegetables (continuous), red meat (continuous), dietary calcium intake (continuous), alcohol (continuous), and menopausal hormone therapy in women (yes or no). *P* values for linear trends were calculated by using median values within quintiles. All statistical tests were 2-sided and considered significant at $P < 0.05$; analyses were conducted with SAS software (version 9.1.3; SAS Institute).

defined population. The number of incident colorectal cancers was slightly higher in the current study ($n = 6946$) than in either the pooling project ($n = 5604$) or a recent meta-analysis ($n = 5403$).

We observed differences by anatomic subsites in our study because associations appeared stronger for the proximal than for the distal colon and appeared only for rectal cancer with decaffeinated coffee. In general, previous studies of coffee and tea intakes have not observed substantial differences by subsites, but the studies had small cases numbers (31, 32, 34, 35, 38, 39). Although our findings require replication, subsite differences have been observed for other colorectal cancer risk factors, including adult height, aspirin use, physical activity, and meat intake (17–22). Subsites within the colorectum have distinct embryonic origins,

TABLE 3
HRs for colorectal cancer by tea intake in the NIH-AARP Diet and Health Study[1]

	All tea		Caffeinated tea		Decaffeinated tea	
Outcome	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Colorectal	6905	—	6905	—	6905	—
None	2322	1.00	3853	1.00	5762	1.00
<1 cup/mo	1236	0.90 (0.84, 0.97)	794	0.91 (0.84, 0.99)	209	0.92 (0.80, 1.06)
1–3 cups/mo	1143	0.95 (0.88, 1.02)	799	0.96 (0.89, 1.04)	279	0.95 (0.84, 1.07)
1–6 cups/wk	1144	0.93 (0.86, 1.00)	767	0.99 (0.91, 1.08)	332	0.82 (0.73, 0.92)
≥1 cup/d	1060	0.97 (0.90, 1.05)	692	1.00 (0.91, 1.09)	323	0.93 (0.83, 1.05)
P-trend	—	0.700	—	0.300	—	0.300
Colon	5044	—	5044	—	5044	—
None	1666	1.00	2829	1.00	4164	1.00
<1 cup/mo	906	0.91 (0.84, 0.99)	578	0.92 (0.84, 1.01)	162	0.98 (0.83, 1.15)
1–3 cups/mo	843	0.96 (0.89, 1.05)	578	0.96 (0.87, 1.06)	216	1.00 (0.87, 1.16)
1–6 cups/wk	841	0.94 (0.86, 1.02)	551	0.98 (0.89, 1.08)	257	0.86 (0.76, 0.99)
≥1 cup/d	788	0.99 (0.91, 1.08)	508	1.01 (0.91, 1.11)	245	0.96 (0.84, 1.11)
P-trend	—	0.500	—	0.400	—	0.700
Proximal colon	2846	—	2846	—	2846	—
None	931	1.00	1579	1.00	2347	1.00
<1 cup/mo	512	0.90 (0.81, 1.01)	330	0.93 (0.82, 1.05)	94	0.96 (0.77, 1.19)
1–3 cups/mo	473	0.94 (0.84, 1.05)	317	0.92 (0.81, 1.05)	125	0.98 (0.81, 1.19)
1–6 cups/wk	473	0.90 (0.80, 1.01)	304	0.94 (0.82, 1.07)	156	0.88 (0.74, 1.04)
≥1 cup/d	457	0.98 (0.88, 1.10)	316	1.08 (0.95, 1.23)	124	0.81 (0.67, 0.98)
P-trend	—	0.600	—	0.080	—	0.060
Distal colon	1983	—	1983	—	1983	—
None	656	1.00	1125	1.00	1638	1.00
<1 cup/mo	363	0.95 (0.83, 1.08)	227	0.93 (0.80, 1.08)	62	1.01 (0.78, 1.32)
1–3 cups/mo	333	1.00 (0.87, 1.14)	234	1.01 (0.87, 1.17)	82	1.03 (0.82, 1.30)
1–6 cups/wk	331	0.98 (0.86, 1.12)	226	1.05 (0.90, 1.23)	87	0.80 (0.64, 1.01)
≥1 cup/d	300	1.02 (0.88, 1.17)	171	0.90 (0.76, 1.07)	114	1.24 (1.01, 1.52)
P-trend	—	0.600	—	0.400	—	0.050
Rectal	1861	—	1861	—	1861	—
None	656	1.00	1024	1.00	1598	1.00
<1 cup/mo	330	0.87 (0.76, 1.00)	216	0.89 (0.77, 1.04)	47	0.76 (0.57, 1.03)
1–3 cups/mo	300	0.91 (0.79, 1.05)	221	0.97 (0.83, 1.13)	63	0.79 (0.61, 1.03)
1–6 cups/wk	303	0.91 (0.79, 1.05)	216	1.02 (0.88, 1.20)	75	0.69 (0.54, 0.88)
≥1 cup/d	272	0.92 (0.80, 1.07)	184	0.97 (0.82, 1.14)	78	0.84 (0.66, 1.07)
P-trend	—	0.800	—	0.600	—	0.200

[1] HRs and 95% CIs were estimated by using Cox proportional hazards regression models with person-years as the underlying time metric adjusted for age (continuous), sex, race (non-Hispanic white, non-Hispanic black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown), education (<11 y or unknown, high school graduate, some college, or college graduate), smoking status (never, former, or current), time since quitting for former smokers, smoking dose, ever smoke a pipe or cigar, diabetes (yes or no), colorectal screening (yes or no), family history of colorectal cancer (yes or no), regular nonsteroidal antiinflammatory drug use (yes or no), marital status (married: yes or no), BMI (in kg/m^2; <18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35), frequency of vigorous physical activity (never or rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), calories (continuous), fruit and vegetables (continuous), red meat (continuous), dietary calcium intake (continuous), alcohol (continuous), and menopausal hormone therapy in women (yes or no). *P* values for linear trends were calculated by using median values within quintiles. All statistical tests were 2-sided and considered significant at $P < 0.05$; analyses were conducted with SAS software (version 9.1.3; SAS Institute).

genetic mutation spectra, morphologic appearance, and physiologic function (19, 40–43), and these differences may affect susceptibility to environmental risk factors.

In our study, we showed that caffeinated coffee was associated with decreased risk of colon cancer, whereas decaffeinated coffee was associated with decreased risk of both colon and rectal cancers. Observed differences could reflect chance or perhaps residual confounding if lifestyles differed between individuals who drink caffeinated coffee and individuals who drink decaffeinated coffee. In support of this hypothesis, we showed that participants who primarily drank decaffeinated coffee tended to consume less alcohol, fewer calories, and less red meat; eat more fruit and vegetables; exercise less; and smoke more than did participants who primarily drank caffeinated coffee. Michel et al (32) also showed that people who regularly drank decaffeinated coffee were more health conscious in their behaviors than were people who did not. It is also possible that the spectrum of compounds in decaffeinated coffee, including, perhaps, the lack of caffeine, is more beneficial for cancer prevention of the rectum. In any case, future studies are needed to investigate these associations.

The benefits of coffee consumption have been observed for multiple chronic diseases such as diabetes, Parkinson disease, and

TABLE 4
HRs for colon cancer by coffee intake stratified by selected covariates[1]

Selected covariates	None	<1 cup/wk	1 cup/d	1–3 cups/d	4–5 cups/d	≥6 cups/d	*P*-trend	*P*-interaction
Sex[2]								0.6
Men (*n*)	280	525	544	1505	400	116	—	
HR (95% CI)	1.00	1.00 (0.86, 1.15)	0.96 (0.83, 1.12)	0.97 (0.86, 1.11)	0.83 (0.71, 0.97)	0.77 (0.62, 0.96)	0.001	
Women (*n*)	211	270	343	672	170	36	—	
HR (95% CI)	1.00	0.85 (0.71, 1.02)	0.98 (0.82, 1.16)	0.92 (0.78, 1.08)	0.91 (0.74, 1.12)	0.64 (0.45, 0.92)	0.1	
Smoking[3]								0.5
Never (*n*)	254	288	311	575	102	14	—	
HR (95% CI)	1.00	0.87 (0.74, 1.03)	0.97 (0.82, 1.15)	1.00 (0.86, 1.16)	0.88 (0.70, 1.11)	0.61 (0.35, 1.04)	0.4	
Former (*n*)	173	416	471	1266	328	72	—	
HR (95% CI)	1.00	1.07 (0.90, 1.28)	1.04 (0.87, 1.24)	1.03 (0.88, 1.20)	0.93 (0.77, 1.12)	0.75 (0.57, 0.98)	0.004	
Current (*n*)	47	52	67	257	119	59	—	
HR (95% CI)	1.00	0.62 (0.42, 0.92)	0.68 (0.47, 0.99)	0.61 (0.44, 0.83)	0.53 (0.38, 0.75)	0.53 (0.36, 0.78)	0.01	
Diabetes[4]								0.7
No diabetes (*n*)	420	693	774	1922	509	137	—	
HR (95% CI)	1.00	0.96 (0.85, 1.08)	0.99 (0.88, 1.11)	0.96 (0.87, 1.07)	0.86 (0.75, 0.98)	0.74 (0.61, 0.90)	0.0005	
Diabetes (*n*)	71	102	113	255	61	15	—	
HR (95% CI)	1.00	0.83 (0.61, 1.12)	0.87 (0.64, 1.17)	0.91 (0.69, 1.19)	0.81 (0.57, 1.15)	0.71 (0.40, 1.25)	0.4	
BMI[5]								0.7
18.5 to <25 kg/m^2 (*n*)	156	225	275	576	160	47	—	
HR (95% CI)	1.00	0.88 (0.71, 1.08)	0.97 (0.80, 1.19)	0.85 (0.71, 1.02)	0.78 (0.62, 0.98)	0.74 (0.52, 1.03)	0.02	
≥25 kg/m^2 (*n*)	322	535	584	1529	392	102	—	
HR (95% CI)	1.00	0.95 (0.83, 1.09)	0.96 (0.83, 1.10)	0.98 (0.86, 1.10)	0.86 (0.74, 1.00)	0.73 (0.59, 0.92)	0.006	
Red meat intake[6]								0.2
Low (*n*)	255	421	451	922	224	55	—	
HR (95% CI)	1.00	0.94 (0.80, 1.10)	1.00 (0.85, 1.16)	0.90 (0.78, 1.04)	0.80 (0.66, 0.96)	0.68 (0.50, 0.92)	0.0006	
High (*n*)	236	374	436	1255	346	97	—	
HR (95% CI)	1.00	0.94 (0.80, 1.10)	0.94 (0.80, 1.10)	1.00 (0.87, 1.15)	0.89 (0.76, 1.06)	0.78 (0.61, 0.99)	0.09	

[1] HRs and 95% CIs were estimated by using Cox proportional hazards regression models with person-years as the underlying time metric adjusted for age (continuous), sex, race (non-Hispanic white, non-Hispanic black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown), education (<11 y or unknown, high school graduate, some college, or college graduate), smoking status (never, former, or current), time since quitting for former smokers, smoking dose, ever smoke a pipe or cigar, diabetes (yes or no), colorectal screening (yes or no), family history of colorectal cancer (yes or no), regular nonsteroidal antiinflammatory drug use (yes or no), marital status (married: yes or no), BMI (in kg/m^2; <18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35), frequency of vigorous physical activity (never or rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), calories (continuous), fruit and vegetables (continuous), red meat (continuous), dietary calcium intake (continuous), alcohol (continuous), and menopausal hormone therapy in women (yes or no). *P* values for linear trends were calculated by using median values within quintiles. All statistical tests were 2-sided and considered significant at $P < 0.05$; analyses were conducted with SAS software (version 9.1.3; SAS Institute).

[2] Models did not include sex.

[3] Models did not include smoking variables.

[4] Models did not include diabetes.

[5] Models did not include BMI.

[6] Models did not include red meat (low categorized as below the median and high categorized as above the median).

liver and prostate cancers (1–6, 44, 45). Phytochemicals in coffee exhibit several anticarcinogenic properties (5, 46) and include the diterpenes cafestol and kahweal, which induce phase I and II enzyme activities (47–49); polyphenols, such as flavonoids (50); and chlorogenic acid, which can affect insulin and glucose response (5) and has antioxidant properties (50). However, future mechanistic work is needed because coffee has many components, and effects may depend on multiple factors (eg, the type of coffee bean, caffeinated compared with decaffeinated coffee, roasting, and brewing methods (eg, boiled unfiltered coffee contains smaller amounts of lipid-containing diterpenes than filtered coffee does) (10, 13, 51, 52). Also, coffee constituents (ie, ferulic acid and chrologenic acid) are metabolized by gut bacteria to form active metabolites (53–56). Future epidemiologic studies should assess coffee types and methods of preparation and collect biological samples (eg, blood, urine, saliva, and feces) to elucidate the relation between specific phytochemicals in coffee and colorectal cancer risk.

Although cancer-prevention trials with green tea polyphenols have shown promising results, epidemiologic studies have not provided support (16, 32, 37, 57, 58). Results from individual prospective cohorts were generally null (32, 57–59), although a recent pooled analysis of 13 prospective studies showed a positive association between tea intake and colorectal cancer (16). Explanations for differences between our null findings and pooling-project results are unclear, although we lacked many heavy tea drinkers in our study, which may have precluded us from observing an association. Results in our study for decaffeinated tea differed by colon cancer subtypes. Although these findings were likely due to chance, we lacked information on whether decaffeinated tea was black, green, or herbal. Future studies in heavy tea-drinking populations are needed.

Strengths of our study were its large size, prospective design, and wide range of coffee consumption, which allowed us to investigate associations by subsites within a single cohort using a standardized protocol. Study limitations included the self-report

of coffee- and tea-drinking habits as well as the assessment of intakes at a single time point. We also lacked an assessment of preparation methods, which likely affect the concentration of different compounds in coffee (36, 51, 52). Caffeinated and decaffeinated coffee drinkers were also defined on the basis of their drinking either beverage more than one-half of the time, which could have led to misclassification. The potential for residual confounding was also a possible concern, despite the care taken to adjust for known confounders. Cigarette smoking and red-meat consumption are correlated with coffee drinking, and they are both associated with colorectal cancer; to account for this, we carefully adjusted for these factors, and we noted that results for coffee were generally similar in never, former, and current smokers. The beneficial effect of coffee intake on colon cancer was confined to the first 6 y of follow-up and attenuated in the latter 4 y, which suggested that the baseline consumption may have more accurately reflected the earlier rather than the later follow-up period. Attenuated findings in participants who developed colorectal cancer >6 y after baseline could have been due to chance, changes in coffee drinking over this time period, or reverse causality. We could not rule out reverse causality because we did not collect information on inflammatory bowel disease or other conditions that may have caused participants to reduce or eliminate coffee consumption that may also be associated with colorectal cancer. A similarly attenuated association was observed in an 8-y lag analysis of coffee intake and prostate cancer in the Health Professionals Follow-Up Study (6).

Caution should be applied when attempting to generalize our findings to other populations because our cohort was predominantly non-Hispanic white, was college educated, and, overall, may have had a healthier lifestyle than that of similarly aged adults in the US population. However, it seems likely that the biologic mechanisms relating coffee intake to colorectal cancer would apply to multiple populations.

In conclusion, in this large US prospective cohort, predominantly caffeinated coffee drinkers had a significantly lower risk of colon cancer, particularly proximal tumors, whereas predominantly decaffeinated coffee drinkers had a decreased risk of both colon and rectal cancers. No associations were shown for tea. Additional investigations that evaluate associations of coffee and its components with colorectal cancer subtypes are warranted.

Cancer-incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer-incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer-incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer-incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. Cancer-incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer-incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer-incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer-incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health. Cancer-incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer-incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. Cancer-incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, State of Nevada Department of Health and Human Services.

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