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Coffee consumption and risk of colorectal cancer: A systematic review and meta-analysis of prospective cohort studies

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An inverse association between coffee consumption and the risk of colorectal cancer has been found in several case-control studies, but such an association was not consistent in prospective cohort studies. We conducted a systematic meta-analysis of prospective cohort studies on coffee consumption and colorectal cancer published up to June 2008. We combined relative risks (RR) for colorectal cancer comparing high *vs.* low categories of coffee consumption using random-effects models. We identified 12 eligible cohort studies, which included 646,848 participants and 5,403 cases for colorectal cancer. The summarized result of the meta-analysis comparing high- *vs.* low-consumption categories showed no significant effect of coffee consumption on colorectal cancer risk (RR = 0.91; 95% confidence intervals [CI]: 0.81–1.02). The RR was 0.93 (95% CI: 0.71–1.22) when considering 4 studies conducted in the United States of America, 0.91 (95% CI: 0.76–1.10) for 5 studies from Europe, and 0.83 (95% CI: 0.62–1.10) for 3 Japanese studies. No significant differences by sex and cancer-site were found, but there was a slight suggestion of an inverse association between coffee consumption and colon cancer in women (RR = 0.79; 95% CI: 0.60–1.04), especially Japanese women (RR = 0.62; 95% CI: 0.37–1.05). The suggestive inverse associations were slightly stronger in studies that controlled for smoking and alcohol, and in studies with shorter follow-up times. Information on coffee type, its serving size, or brewing method may provide a better understanding of this reassuring result and the real role of coffee on colorectal cancer risk.
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Key words: caffeine; coffee; colorectal neoplasms; meta-analysis; prospective studies

Colorectal cancer is the third most common cancer worldwide.[1] Although obesity, smoking, alcohol, and physical inactivity are important risk factors for colorectal cancer, nutritional factors are also considered to play an important role for its development.[2] The relationship between coffee consumption and colorectal cancer risk has been extensively examined over the last 4 decades.[3] Coffee is a complex mixture of more than a thousand chemicals, and these constituents have potential genotoxic and mutagenic properties, but also antioxidant and antimutagenic activities,[4,5] any of which could affect colorectal cancer risk. Several case-control studies have shown an inverse association between coffee consumption and risk of colorectal cancer. A meta-analysis, combining the results of 12 case–control studies, found an odds ratio of 0.72 (95% confidence interval [CI]: 0.61–0.84) for high *vs.* low coffee intake, but the combination of 5 cohort studies demonstrated no association (relative risk [RR] = 0.97; 95% CI: 0.73–1.29).[6] Although the data from case-control studies are relatively consistent, they may be subject to recall bias with respect to coffee consumption and selection bias with respect to the control group. Additional prospective cohort studies excluding those biases would be more useful to see coffee-colorectal cancer associations. Since the first meta-analysis was conducted in 1998, more results from prospective cohort studies have been reported in USA,[7] Europe,[8–10] and Japan,[11–13] and most of the studies reported sex- and cancer site-specific relative risks.

We therefore systematically reviewed and performed a meta-analysis of prospective cohort studies to quantitatively assess the association between coffee consumption and colorectal cancer in men and women. Because of the high consumption of coffee, even small effects on colorectal cancer in persons could have a large impact on public health.

Material and methods

Study identification

We searched the MEDLINE database to identify eligible studies published in English through June 2008. The reference lists of retrieved articles were additionally hand-searched. For computer searches, we used the following Medical Subject Heading (MeSH) and/or text words in any field: "(caffeine or coffee) combined with (colorectal or colon or rectal neoplasms)." Studies were included in the meta-analyses if they presented data from prospective cohort studies on the association between coffee consumption and colorectal cancer incidence.

Data extraction and classification

Data abstraction was conducted independently by 2 investigators (Y. J. and W. L.) according to the meta-analysis of observation studies in epidemiology (MOOSE) guidelines,[14] and discrepancies were adjudicated. For each study, the following information was extracted: first author's last name; year of publication; country of origin; follow-up period; number of subjects and cases; age at baseline; RRs and 95% CIs for the association between coffee consumption (as cups per day) and colorectal cancer incidence, considering 2 exposure levels (low *vs.* high) or per unit increase in exposure; and control of confounding factors.

If 95% CIs were not reported, but numbers of cases and controls in high *vs.* low categories of coffee consumption were provided, these data were used to calculate a standard error of the crude odds ratio, and then approximate CIs for the reported adjusted odds ratios.[15] If RRs were reported as per unit increase in coffee consumption, we calculated RRs and 95% CIs for a 5-cup increment[16] and a 6-cup increment,[17] respectively, which were the means of the upper coffee categories of 3 studies from the USA,[7a,7b,18] and 4 studies from Europe.[8–10,15] If a study provided several RRs, we extracted the RRs reflecting the greatest degree of control for potential confounders.[10–13] When a study provided RRs for both colorectal cancer and invasive colorectal cancer, we used the former, which had more cases.[13] One study reported pooled estimates from 2 large cohorts, Swedish Mammography Cohort (SMC, 1987–2004) and Cohort of Swedish Men (COSM, 1998–2004), and reported additional pooled estimates by starting follow-up in 1998 for the SMC.[10] We extracted the latter pooled estimates (1998–2004 for both cohorts). Although there is 1 report conducted on the same cohort (SMC), we included the study because it was conducted during the different period (1987–1998).[9] One report provided separate RRs from 2 large US cohorts, the Nurses' Health Study (NHS)[7a] and the Health Profes-

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sionals Follow-up Study (HPFS),[7b] and we counted the report as 2 prospective studies.[7a,7b]

Statistical analysis

We pooled the RRs for high *vs.* low categories of coffee consumption from each study. To estimate a summary RR for colorectal cancer in both sexes combined, we used combined estimates if provided. Otherwise, we included all estimates according to sex and/or cancer site in the analysis as if obtained from different studies. Summary measures were calculated using random-effects models[19] that consider both within-study and between-study variations. Statistical heterogeneity among studies included in the meta-analysis was assessed using the Q statistic,[20] and inconsistency was quantified with the I^2 (I-squared) statistic.[21]

Various sources of heterogeneity likely exist due to international differences in coffee consumption (*e.g.*, serving size, coffee type, or brewing method) in this analysis. To examine the magnitude of the combined RR in each stratum and its respective test of heterogeneity, we conducted subgroup analyses by geographic regions (United States, Europe, or Japan), cancer sites (colon or rectum), and gender. To test for variation in risk estimates by those variables and examine other sources of heterogeneity (*e.g.*, publication year, follow-up period), we conducted meta-regression analyses. In addition, sensitive analyses were conducted by limiting the analysis to studies that had adjusted for smoking and alcohol. Only 6 of the 12 studies met this criterion.[7a,7b,11–13,16] Finally, publication bias was evaluated through funnel plots (*i.e.*, plots of study results against precision) and with the Begg's[22] and Egger's tests.[23] $p < 0.05$ was considered statistically significant. All statistical analyses were performed by using Stata version 9.2 software (Stata Corporation, College Station, Texas).

Results

Characteristics of studies

We identified a total of 12 prospective cohort studies including 646,848 participants and 5,403 incident cases of colorectal cancer that were potentially eligible for inclusion in the meta-analysis.[7–13,15–18] The characteristics of the included studies are summarized in Table I. Four of these studies were conducted in the United States (n = 1,833 cases),[7a,7b,16,18] whereas 5 were in Europe (n = 1,737 cases),[8–10,15,17] and 3 in Japan (n = 1,833 cases).[11–13] One study conducted in the United States did not provide site-specific RRs,[18] and 1 study reported RRs only for colon cancer.[11] Eleven of these studies, therefore, were used for colon cancer (n = 3,730 cases),[7–13,15–17] and 10 were used for rectal cancer (n = 1,543 cases).[7–10,12,13,16–18] By sex, 7 of these studies provided RRs for colorectal cancer in men (n = 2,035 cases),[7a,8,11–13,17,18] and women (n = 2,216 cases).[7b,9,11–13,17,18]

High vs. *low categories of coffee consumption*

The combined results from 12 studies found a RR of 0.91 (95% CI: 0.81–1.02) comparing high *vs.* low coffee consumption categories for colorectal cancer (Fig. 1). Results stratified by cancer site and geographic region are shown in Table II. By geographic region, Japanese studies showed a tendency toward a lower risk of colorectal cancer with higher coffee consumption (RR = 0.83; 95% CI: 0.62–1.10). By cancer site, colon cancer tended to show a weak inverse association (RR = 0.90; 95% CI: 0.78–1.04), while rectal cancer showed no association (RR = 0.98; 95% CI: 0.80–1.20). Although no significant difference by geographic region was found in each cancer site, a lower risk of colon cancer was slightly suggested among Japanese studies (RR = 0.80; 95% CI: 0.57–1.12). There was no statistically significant heterogeneity among all cohort studies (p for heterogeneity = 0.73; I^2 = 0%). However, there was some evidence of heterogeneity among studies conducted in Japan (p for heterogeneity = 0.10; I^2 = 48%). Even after stratified by cancer site, some heterogeneity still existed for colon cancer among Japanese studies (p for heterogeneity = 0.10; I^2 = 49%).

Compared to men, women tended to show a lower risk of colorectal cancer (RR = 0.85; 95% CI: 0.69–1.05), colon cancer (RR = 0.79; 95% CI: 0.60–1.04), but not for rectal cancer (Table III). The risk was lowest among Japanese women. Overall, there was no significant difference by sex in any cancer sites and regions. The studies conducted in Japan showed a nonsignificant sex disparity for colon cancer (p for difference = 0.12). Although Japanese studies showed some tendency of heterogeneity for colon cancer, it disappeared when stratified by sex (for men: p for heterogeneity = 0.55, I^2 = 0%; for women: p for heterogeneity = 0.23, I^2 = 32%; data not shown).

We conducted meta-regression analyses to investigate whether publication year or length of follow-up affects the association between coffee consumption and colorectal cancer. The year of publication did not have a statistically significant effect on the summary RR for colorectal, colon or rectal cancer (all p values > 0.20). For duration of follow-up, we used 10 years of follow-up time as a cutoff because the mean of follow-up times for all 12 studies was approximately 9.8 years. The studies with short follow-up times (<10 years)[8–11,16,18] showed a more inverse association between coffee consumption and colorectal cancer, compared to those with long follow-up times (≥10 years)[7a,7b,12,13,15,17] (Table IV). When we included an interaction term for coffee consumption and study length of follow-up, each additional year of follow-up was associated with a slightly positive association between coffee consumption and rectal cancer (8% increased risk, ranging 0 to 17%; p = 0.05). This result indicated that studies with shorter follow-up had more suggestion of an inverse association, but this was attenuated in studies with longer follow-up time.

When the analysis was limited to the studies that had adjusted for potential confounders including smoking and alcohol, the summary RRs of colorectal and colon cancers decreased to 0.85 (95% CI: 0.70–1.03)[7a,7b,11–13,16] and 0.85 (95% CI: 0.67–1.07),[7a,7b,11–13,16] respectively, whereas the risk of rectal cancer slightly increased to 1.07 (95% CI: 0.80–1.44)[7a,7b,12,13,16] (Table IV).

Publication bias

There was no evidence of publication bias in the literature on coffee consumption and colorectal cancer, colon or rectal cancer in men or women (all p values from the Begg's and Egger's tests > 0.4). For the overall analysis of colorectal cancer in both sexes combined, the Egger regression asymmetry test suggested some evidence of bias (p value for bias = 0.03), but the evidence of bias was not shown in the Begg's test (p value for bias = 0.08). The difference in the results obtained from the 2 methods may be due to a greater statistical power of the regression method.[24] In the stratified analysis by cancer site, there was some evidence of bias for colon cancer (p value for bias = 0.02 in both tests), indicating that stronger associations between high coffee consumption and colon cancer tended to be observed for smaller studies, but the evidence for bias was not detected for rectal cancer (p values for bias = 0.15 from the Begg's test, and 0.19 from the Egger's test).

Discussion

This meta-analysis of prospective cohort studies indicates that coffee drinkers were not found to be at substantially decreased risk of colorectal, colon or rectal cancer. However, women who drank an average coffee intake of 4 or more cups per day had a marginally lower incidence of colon cancer than those who reported that they rarely or never drank coffee.

Our meta-analysis for colorectal cancer used the combined data from all 12 prospective cohort studies containing 5,403 cases, which provides more precise risk estimates than the previous meta-analysis[6] containing only 931 cases from 5 cohort studies.[15–18,25] We excluded one of the 5 cohort studies, which used mortality as an endpoint,[25] since mortality studies might be

TABLE I – CHARACTERISTICS OF COHORT STUDIES OF COFFEE CONSUMPTION AND COLORECTAL CANCER RISK

First author (year)	Country	Follow-up period[1]	Study subjects	No. of cases	RR (95% CI)	Coffee ("high" *vs.* "low")	Adjustment factors
Jacobsen, (1986)[15]	Norway	1967–1978 (11.5)	13,664 M 2,891 F Aged ≥35 y	97 CC 63 RC	0.54 (0.22–1.30)[2] 1.07 (0.41–2.79)[2]	≥7 cups/d *vs.* ≤2 cups/d	Age, sex, alcohol for CC, residence
Wu, (1987)[18]	United States (Retirement Community)	1981–1985 (4.5)	11,644	58 CRC (M) 68 CRC (F)	1.54 (0.6–3.7) 1.17 (0.4–3.1)	≥4 cups/d *vs.* ≤1cup/d	Age
Klatsky, (1988)[16]	United States	1978–1984	106,203	203 CC 66 RC	0.92 (0.80–1.06) 0.84 (0.66–1.07)	Continuous variable (cups/d)	Age, sex, alcohol, smoking, BMI, race, education, serum cholesterol,
Stensvold, (1994)[17]	Norway	1977–1990 (10.1)	21,735 M 21,238 F Aged 35–54 y	78 CC (M) 52 CC (F) 41 RC (M) 38 RC (F)	0.98 (0.81–1.19) 0.96 (0.74–1.25) 0.92 (0.71–1.20) 0.86 (0.63–1.17)	Continuous variable (cups/d)	Age, sex, smoking, residence
Hartman, (1998)[8]	Finland (A Finish Clinical Trial Cohort)	1985–1993 (8.0)	27,111 M Aged 50–69 y smokers	106 CC 79 RC	0.84 (0.50–1.40) 0.74 (0.40–1.36)	>6 cups/d *vs.* ≤4 cups/d	Age, BMI, physical activity, intervention group, serum cholesterol for RC, calcium, tea
Terry, (2001)[9]	Sweden (Swedish Mammography Cohort)	1987–1998 (9.6)	61,463 F Aged 40–74 y	460 CRC 291 CC 159 RC	1.04 (0.70–1.54) 1.06 (0.65–1.72) 1.06 (0.54–2.10)	≥4 cups/d *vs.* <1cup/d	Age, alcohol, BMI, education, calories, red meat, fat, fiber, calcium, folic acid, vitamin C, vitamin D
Michels, (2005)[7a]	United States (Health Professionals' Follow-up Study)	1986–1998	46,099 M Aged 40–75 y	n/a CRC 446 CC 106 RC	1.09 (0.55–2.17) 1.39 (0.69–2.78 1.33 (0.69–2.56)	>5 cups/d *vs.* never (CC) ≥4 cups/d *vs.* never (RC)	Age, BMI, height, alcohol, smoking, physical activity, family history of CRC, sigmoidoscopy, aspirin use, vitamin supplement, calories, red meat
Michels, (2005)[7b]	United States (Nurses' Health Study)	1980–1998	87,794 F Aged 34–59 y	n/a CRC 731 CC 155 RC	0.94 (0.63–1.40) 0.85 (0.55–1.32) 1.80 (0.94–3.44)	>5 cups/d *vs.* never (CC) ≥4 cups/d *vs.* never (RC)	Age, BMI, height, alcohol, smoking, physical activity, family history of CRC, sigmoidoscopy, aspirin use, vitamin supplement, calories, red meat, menopausal status, postmenopausal hormone use
Larsson (2006)[10]	Sweden (Swedish Mammography Cohort and Cohort of Swedish Men)	1998–2004	45,306 M Aged 45–79 y 36,616 F Aged 51–87 y	723 CRC 469 CC 256 RC	1.06 (0.74–1.52) 1.16 (0.73–1.85) 0.92 (0.51–1.65)	≥6 cups/d *vs.* <1 cup/d	Age, BMI, smoking, physical activity, family history of CRC and diabetes, aspirin use, multivitamin use, calories, red meat, fruits, vegetables, milk, for women post menopausal hormone use

TABLE I – CHARACTERISTICS OF COHORT STUDIES OF COFFEE CONSUMPTION AND COLORECTAL CANCER RISK (CONTINUED)

First author (year)	Country	Follow-up period[1]	Study subjects	No. of cases	RR (95% CI)	Coffee ("high" *vs.* "low")	Adjustment factors
Oba, (2006)[11]	Japan	1993–2000	13,894 M 16,327 F Aged ≥35 y	111 CC (M) 102 CC (F)	0.81 (0.46–1.42) 0.43 (0.22–0.85)	≥1 cup/d *vs.* <1 cup/month	Age, BMI, height, alcohol, smoking, physical activity, black/green tea
Naganuma, (2007)[12]	Japan (Miyagi Cohort Study)	1990–2001 (11)	18,867 M 19,834 F Aged 40–64 y	284 CRC (M) 173 CRC (F) 175 CC (M) 106 CC (F) 112 RC (M) 68 RC (F)	0.91(0.56–1.46) 1.16 (0.60–2.23) 0.91 (0.49–1.69) 1.16 (0.47–2.88) 0.92 (0.45–1.90) 1.08 (0.42–2.82)	≥3 cups/d *vs.* never	Age, sex, BMI, alcohol, smoking, walking time, family history of CRC, education, calories, fruits, vegetables, meat, black/green tea, for women menopausal status, numbers of pregnancies and deliveries, age at menarche, age at first delivery
Lee, (2007)[13]	Japan (Japan Public Health Center-based Prospective Study)	1990–2002 (10)	46,023 M Aged 51.9 y 50,139 F Aged 52.3 y	726 CRC (M) 437 CRC (F) 477 CC (M) 286 CC (F) 249 RC (M) 151 RC (F)	1.10 (0.82–1.47) 0.68 (0.40–1.15) 1.15 (0.80–1.66) 0.60 (0.31–1.19) 1.01 (0.61–1.66) 0.84 (0.36–1.94)	≥3 cups/d vs. almost never	Age, BMI, alcohol, smoking, physical activity, study area, family history of CRC, beef, pork, green vegetables, black/green tea, Chinese tea

[1]Mean or median duration of follow-up in parenthesis.– [2]Standard error calculated from data.
CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; BMI, body mass index; RR, relative risk; CI, confidence interval.

influenced by survival after diagnosis. The excluded study was targeted on a unique population of Adventist religious adherents in the USA. Since the study showed a positive association between coffee intake and colorectal cancer (RR = 1.5; 95% CI: 1.0–2.2), the meta-analysis after inclusion of the study resulted in a slightly greater RR for colorectal cancer (RR = 0.94; 95% CI: 0.84–1.06; data not shown).

The inclusion of recent large cohort studies in our meta-analysis allowed for separate analyses by cancer site, region, and sex with reasonable statistical power. However, a separate analysis for colon cancer at proximal and distal sites was not conducted due to only a few studies available.[9,12] A clinical study found that coffee intake increased colonic motility, which may reduce colorectal exposure to fecal carcinogens.[26] Since the increased colonic motility was limited to the rectosigmoid region, the subsite-specific analyses warrant further investigation.

Some nondifferential misclassification of self-reported coffee intake is inevitable, which may attenuate any true association between coffee intake and colorectal cancer. However, several studies have shown coffee intake assessed by questionnaire to be valid[27–29] and reproducible.[15,30] Further, intake was assessed only once at baseline in all 5 cohort studies[15–18,25] included in the previous meta-analysis,[6] which could be a limitation if people change their coffee intake substantially during follow-up. For our meta-analysis, we included 2 large US cohort studies (the NHS and the HPFS) containing updated dietary information during follow-up,[7a,7b] which can more precisely estimate long-term coffee intake.

The stratified-analysis by follow-up period indicated that studies with shorter follow-up time (<10 years)[8–11,16,18] are more likely to show an inverse association between coffee intake and the risk of colorectal cancer, compared to those with longer follow-up time (≥10 years).[7a,7b,12,13,15,17] Case-control studies tend to examine the effect of coffee intake shortly before diagnosis, while many cohort studies, especially those with very long follow-up time, tend to examine more distant exposure. Our findings for the studies with short follow-up time are consistent with the results of case-control studies, which have consistently shown an inverse association. This may be related to less exposure misclassification in studies with short follow-up time by reducing the possibility of changing their coffee intake during follow-up. The case-control design has some potential methodological biases, including recall or selection biases. These biases and some residual confounding may in part account for a stronger inverse association in the case-control studies.

Possibly, preclinical colorectal cancer status may have affected coffee intake in cohort studies. For example, individuals who have symptoms from undiagnosed cancer of the large bowel tend to avoid their coffee intake. However, the exclusion of the first 2 years[8,10,13,17] 3 years,[9,11,12] or 4 years[15] of follow-up periods did not substantially change the results, suggesting that it is unlikely that undiagnosed early stages of colorectal cancer influenced responses to dietary questions regarding coffee intake.

The cutoffs for low and high exposure categories varied between studies included in our meta-analysis. Some studies in Europe used 6 or more cups per day as the highest category of coffee intake,[8,10,15] while 1 Japanese study used only 1 or more cups per day.[11] Differences in the selection of a reference group also may account for the differences in the results of the studies. For an exposure with such a wide range of intake among studies, examining RR comparing highest *vs.* lowest levels may be sub-optimal. However, RRs per unit increase in coffee intake (*e.g.*, per 1cup/d) could not be estimated due to the lack of data from original studies.

Most of the studies included in our meta-analysis did not provide information on coffee type, serving size, or brewing method. Only 2 studies from the United States reported separate RRs for caffeinated and decaffeinated coffees,[7a,7b] and when both cohorts combined, there was a significant inverse association between decaffeinated coffee intake and rectal cancer by 52%.[7a,7b] Only a

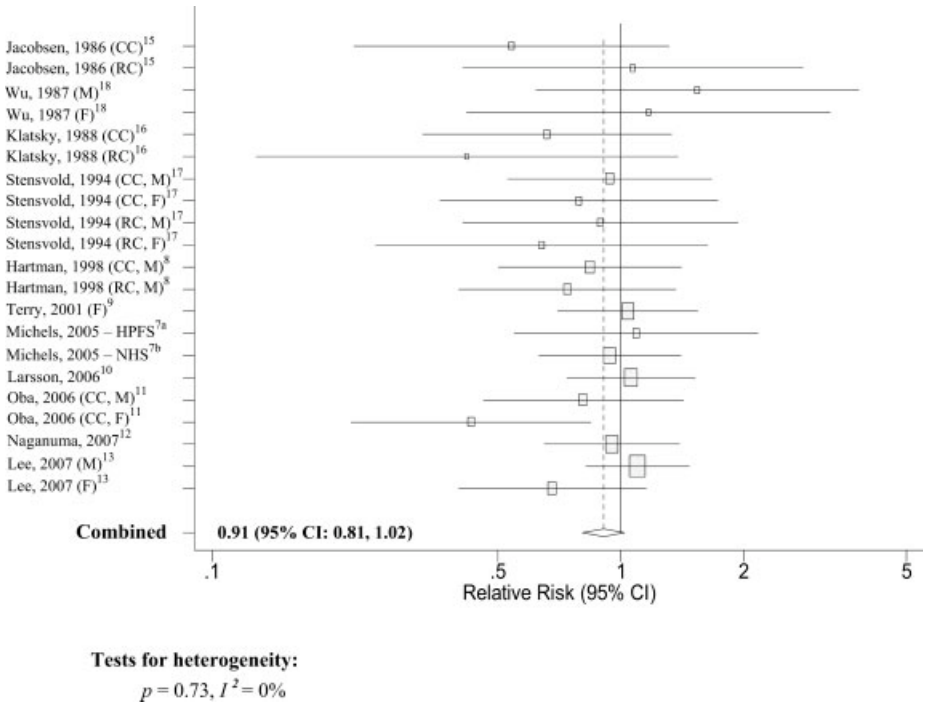

FIGURE 1 – Forest plot of studies of the risk of colorectal cancer for "high" *vs.* "low" coffee consumption. The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis. The combined relative risk is calculated using the random effects method.

TABLE II – SUMMARY OF RISK ESTIMATES OF COFFEE CONSUMPTION WITH COLORECTAL CANCER ACCORDING TO CANCER SITE AND GEOGRPHIC REGION

	No. of studies	No. of cases	Relative risk (95% CI)	Heterogeneity	
				p	I^2 (%)[1]
Colorectal cancer	12	5,403	0.91 (0.81–1.02)	0.73	0
United States	4	1,833	0.93 (0.71–1.22)	0.52	0
Europe	5	1,737	0.91 (0.76–1.10)	0.93	0
Japan	3	1,833	0.83 (0.62–1.10)	0.10	48
Colon cancer	11	3,730	0.90 (0.78–1.04)	0.43	2
United States	3	1,380	0.90 (0.63–1.30)	0.32	14
Europe	5	1,093	0.94 (0.75–1.19)	0.72	0
Japan	3	1,257	0.80 (0.57–1.12)	0.10	49
Rectal cancer	10	1,543	0.98 (0.80–1.20)	0.70	0
United States	3	327	1.17 (0.59–2.31)	0.11	55
Europe	5	636	0.88 (0.65–1.17)	0.94	0
Japan	2	580	0.95 (0.68–1.35)	0.93	0

[1]I^2 is interpreted as the proportion of total variation across studies that is due to heterogeneity rather than chance.

TABLE III – SEX-SPECIFIC RISK ESTIMATES OF COLORECTAL CANCER ACCORDING TO CANCER SITE AND GEOGRAPHIC REGION[1]

	Men		Women		p value difference[2]
	No. of studies	RR (95% CI)	No. of studies	RR (95% CI)	
Colorectal cancer	7	0.97 (0.82–1.15)	7	0.85 (0.69–1.05)	0.39
United States	2	1.24 (0.71–2.14)	2	0.97 (0.67–1.40)	0.54
Europe	2	0.85 (0.63–1.14)	2	0.93 (0.67–1.30)	0.69
Japan	3	1.00 (0.80–1.26)	3	0.70 (0.42–1.18)	0.23
Colon cancer	6	1.00 (0.81–1.24)	6	0.79 (0.60–1.04)	0.20
United States[3]	1	—	1	—	
Europe	2	0.88 (0.60–1.30)	2	0.98 (0.65–1.48)	0.76
Japan	3	1.01 (0.77–1.33)	3	0.62 (0.37–1.05)	0.12
Rectal cancer	5	0.96 (0.73–1.28)	5	1.11 (0.78–1.57)	0.56
United States[3]	1	—	1	—	
Europe	2	0.79 (0.49–1.28)	2	0.89 (0.51–1.54)	0.79
Japan	2	0.98 (0.65–1.48)	2	0.94 (0.50–1.76)	0.92

[1]No heterogeneity existed in all the categories for sex-specific analyses.–[2]p values for the difference in the strength of the association between coffee intake and colorectal cancer between men and women.–[3]Because there was only one study of colon and rectal cancer for US men[7a] or women,[7b] summary relative risks could not be calculated.
RR, relative risk; CI, confidence interval.

TABLE IV – SUMMARY RISK ESTIMATES OF COLORECTAL CANCER BY FOLLOW-UP PERIODS AND ADJUSTMENT FACTORS

Stratification by follow-up periods[1]	No. of studies	RR (95% CI)	Heterogeneity	
			p	I^2 (%)[2]
Colorectal cancer				
< 10 years	6	0.86 (0.71–1.05)	0.32	13
≥ 10 years	6	0.93 (0.80–1.10)	0.88	0
Colon cancer				
< 10 years	5	0.84 (0.64–1.10)	0.23	28
≥ 10 years	6	0.94 (0.77–1.14)	0.54	0
Rectal cancer				
< 10 years	4	0.83 (0.59–1.18)	0.57	0
≥ 10 years	6	1.06 (0.83–1.35)	0.68	0
Adjusted for 2 or more potential confounders[3]				
Colorectal cancer	6	0.85 (0.70–1.03)	0.24	23
Colon cancer	6	0.85 (0.67–1.07)	0.18	31
Rectal cancer	5	1.07 (0.80–1.44)	0.32	14

[1]Ten years of follow-up time were used as a cutoff because the mean of follow-up times for all 12 studies was approximately 9.8 years.–[2]I^2 is interpreted as the proportion of total variation across studies that is due to heterogeneity rather than chance.–[3]The analysis was limited to studies that had adjusted for potential confounders including smoking and alcohol.
RR, relative risk; CI, confidence interval.

few case-control studies examined the relationship between decaffeinated coffee and colorectal cancer,[31–33] and these showed a slight inverse association for rectal cancer as well.[32] Serving sizes and brewing methods for coffee can vary substantially within and between countries. The size of standard coffee cups is larger in the United States compared with that in Europe or Japan, and the difference in the strength of coffee brew may compensate for the different serving size between countries.[34] The association between coffee intake and colorectal cancer may be modified by whether it is filtered or unfiltered (boiled) coffee since filtered coffee contains little amount of lipid components of coffee, the diterpenes cafestol and kahweol, which has been reported to have cholesterol-raising effect and anticarcinogenic activity.[35] Since any effect of coffee intake on colorectal cancer risk could vary by regular or decaffeinated coffee and boiled or filtered coffee, further investigation regarding type- and preparation method-specific analyses is warranted.

Smoking and alcohol are potentially the most likely confounders of the relationship between coffee intake and colorectal cancer.[36,37] Coffee intake has been positively associated with smoking,[7,10,12,13,15,17] alcohol,[7,9,12,13,17] physical inactivity,[7,12,13,17] and intakes of red meat,[7,9,12,13] fat,[38] and cholesterol,[17,37] but negatively with vitamin C,[9] folic acid,[9] multivitamin supplement,[7,10] and vegetable,[10,12,13] suggesting that higher coffee intake might be a surrogate for an unhealthier lifestyle that can enhance the risk of colorectal cancer. Our results from the analysis limited to studies that had adjusted for potential confounders including smoking and alcohol[7a,7b,11–13,16] showed a more inverse association between coffee intake and colorectal cancer. Although allowance for several potential confounding risk factors did not substantially change the results in any study,[7a,7b,10,11–13] some residual confounding by those factors may exist, resulting in attenuation of any inverse association.

Several studies reporting findings with respect to coffee intake and colorectal cancer were not included in the meta-analysis simply because relative risk and precision estimates were not available.[39–41] A Japanese study with 18-year of follow-up showed no association between coffee intake and colon caner and a weak suggestion of an inverse association for rectal cancer.[39] Two more studies conducted in Sweden with 14-year of follow-up[40] and Denmark with 18-year of follow-up[41] showed a lower risk of colon cancer for high *vs.* low coffee intake. Overall, the findings from prospective studies not used for the meta-analysis are consistent with a decreased risk of colorectal cancer.

While we cannot rule out the possibility that uncontrolled confounding or bias accounts for the marginally lower risk of colorectal cancer among high coffee consumers, some possible mechanisms have been suggested. The potential protection of coffee against colorectal cancer may be explained in terms of antimutagenic properties of some coffee compounds (*e.g.*, insoluble hemicellulose fiber, high molecular-weight polyphenol)[42]; antioxidant properties of several phenolic compounds found in coffee beans (*e.g.*, chlorogenic acid, caffeic acid,) partly lost during roasting[43,44]; reductions of bile acid (a promoter of colon cancer) secretions into the colon[45] and synthesis by down-regulating the expression of the bile acid homeostatic genes,[46] and the elimination of several carcinogens by the coffee diterpenes cafestol and kahweol[47]; and an increase in colonic motility limited to the rectosigmoid region by both regular and decaffeinated coffee, seen predominantly in women.[26] In addition, coffee intake might also decrease colon cancer risk by reducing the risk of Type 2 diabetes, which is a known risk factor for colorectal cancer.[48,49] One study suggested lower concentrations of C-peptide, a marker of insulin secretion in women who drank >4 cups per day of caffeinated or decaffeinated coffee compared with nondrinkers.[49] Findings from the 2 studies[26,49] may explain the suggestive protective effect of coffee intake among women in our meta-analysis.

In summary, the results of this meta-analysis of 12 prospective cohort studies showed that coffee intake was not significantly associated with colorectal, colon or rectal cancer risk in men and women, but a slight inverse association was suggested in women, in studies of colon rather than rectal cancer, in studies that adjusted for smoking and alcohol, and in studies with shorter follow-up times. Although no significant difference by sex was found for colorectal cancer in any country, the sex disparity was relatively greater among Japanese studies. Although our results indicate that coffee is unlikely to have a strong protective effect on colorectal cancer risk, they are reassuring no adverse effect of coffee associated with colorectal cancer. Future studies need to better account for long-term coffee drinking, carefully control for potential confounders, and account for potential sex and site-specific difference.

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