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Coffee consumption and risk of colorectal cancer: a meta-analysis of case–control studies

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Abstract A meta-analysis of case–control studies on coffee consumption and colorectal cancer risk was conducted. Twenty-four eligible studies published before May 2010 were identified, including a total of 14,846 cases of colorectal, colon or rectal cancer. Compared to non/occasional drinkers, the odds ratios (OR) for drinkers were 0.83 (95% CI 0.73–0.95) for colorectal, 0.93 (95% CI 0.81–1.07) for colon and 0.98 (95% CI 0.85–1.13) for rectal cancer, with significant heterogeneity among studies; the corresponding ORs for the increment of 1 cup/day were 0.94 (95% CI 0.91–0.98), 0.95 (95% CI 0.92–0.98), and 0.97 (95% CI 0.95–0.99). For the highest coffee drinkers, the ORs were 0.70 (95% CI 0.60–0.81) for colorectal cancer, 0.75 (95% CI 0.64–0.88) for colon cancer and 0.87 (95% CI 0.75–1.00) for rectal cancer, when compared to non/low drinkers. The results of this meta-analysis of case–control studies suggest a moderate favorable effect of coffee consumption on colorectal cancer risk. The reduced risk was consistent across study design (hospital vs. population based), geographic area, and various confounding factors considered. It may reflect a real protection but also partly or largely be due to reverse causation, i.e. decreased coffee consumption among cases following the onset of bowel symptoms.

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Keywords Case–control studies · Coffee · Colorectal cancer · Meta-analysis · Systematic review

Introduction

After tea, coffee is the most widespread beverage in the world [1]. Colorectal cancer is the fourth most common cancer in the world in men and the third in women [2]. Given the widespread consumption of coffee and the high incidence of colorectal cancer, any relation between them would have appreciable public health relevance.

In 1991, an IARC Working Group Monograph concluded that, in humans, "there is some evidence of an inverse relationship between coffee drinking and cancer of the large bowel" [1] and the inverse relation has further been confirmed [1, 3]. A meta-analysis based on data published up to June 1997 found an overall relative risk (RR) of 0.76 for high versus low coffee drinkers (95% confidence interval CI 0.66–0.89) [4]. This finding, however, came mostly from case–control studies (RR = 0.72, 95% CI 0.61–0.84), including 5,261 cases, whereas no material association was observed in cohort studies (RR = 0.97, 95% CI 0.73–1.29), at that time including only 931 cases. A subsequent meta-analysis of cohort studies only, published in 2009 and based on 12 studies and 5,403 cases, found a RR of 0.91 for high versus low coffee drinkers, of borderline significance (95% CI 0.81–1.02), with lower RR in studies that controlled for tobacco and alcohol consumption [5]. A pooled analysis of 13 prospective studies found a RR of 1.07 (95% CI: 0.89–1.30) for more than 6 cups of coffee per day [6]. A Chinese prospective study, published after the meta- and pooled analysis, found a protective effect of coffee only in ever smokers [7]. The apparent stronger inverse association

between coffee intake and colorectal cancer risk found in case–control than in cohort studies might depend on some bias in case–control studies. However, the consistent results in different populations and settings are against any such bias. Likewise, major publication bias is unlikely, as negative results have also attracted interest over the last few years [3].

We combined all available data from case–control studies on coffee drinking and colorectal cancer risk in a systematic meta-analysis [8–31], as the recent meta-analysis included only the results of prospective studies [5], and several case–control studies on coffee drinking and colorectal cancer have been published since the 1997 meta-analysis [4].

Materials and methods

Identification, selection, and classification of studies

We performed a MEDLINE search in PubMed of articles published from 1966 to May 2010, using the string "(coffee OR caffeine OR diet OR beverages OR drinks) AND (colon OR rectum OR rectal OR colorectal) AND (cancer OR neoplasm) AND risk", following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [32], and limiting the search to the English language. The PubMed search identified 2,267 articles. From these articles, two of the authors, F.T. (biostatistician) and A.T. (epidemiologist), independently selected articles reporting data on the association of coffee intake with colorectal, colon, and/or rectal cancer risk, from case–control studies only. They also searched in the reference lists of the articles retrieved to obtain other pertinent publications. Abstracts and unpublished results were not included, but no studies were excluded a priori for weakness of design or data quality. No quality score was assigned. We considered 35 articles, and then we applied the following inclusion criteria: (1) a quantitative estimate of the relation [33–37]; (2) at least one of the following: the 95% CI, or standard error, or the distribution of cases and controls in coffee consumption categories, or the *p*-value for the difference of the OR from unity [38–40]. Studies were also excluded if they reported data for caffeine rather than coffee [41], or if they were based on data updated later, or if part of pooled analyses [42, 43]. Finally, our meta-analysis included 24 case–control studies on coffee intake and risk of colorectal cancer.

Full papers were read and for each paper we registered: first author's last name, year of publication, country where the study was conducted, number of cases, type of controls (population/hospital), odds ratios (OR) and 95% CIs for the highest level of consumption, the highest versus the lowest amount of coffee to which the OR referred, and the adjustment factors. Discrepancies were discussed and adjudicated.

In most studies, information on coffee intake was collected as cups/day. We converted in cups/day the cups/week reported in three studies [17, 26, 31], the cups/month of one study [14] and grams/day (80 g approximately equal to one cup) in one study [25].

If a study reported more than one OR, we used the multivariate one adjusted for the larger number of available potential confounding factors. For a few studies reporting the adjusted ORs and not the corresponding 95% CIs [8–11, 14], we used the distribution of cases and controls to calculate the standard errors of the corresponding crude ORs, and then the approximate CIs for the reported adjusted ORs [44]. To obtain colorectal cancer risk estimates, we included only studies reporting both colon (or its anatomical subsites) and rectal cancer estimates, together or separately, and excluded studies with information on only one anatomical site.

The 24 identified studies included a total of 14,846 cases of colorectal, or colon, or rectal cancer. Their main characteristics are described in Table 1. Eighteen studies gave information on colorectal or both colon and rectal cancer separately, for a total of 10,952 cases. Fifteen studies gave information on colon cancer, for a total of 8,283 cases, and 13 on rectal cancer, for a total of 5,078 cases. Of the 24 studies, 7 were conducted in North America (6 studies from the USA [8, 13, 16, 21, 27, 31] and 1 from Canada [28], for a total of 7,021 cases), 3 in Northern Europe (1 from Norway [9], 1 from Denmark [18] and 1 from Sweden [19], for a total of 787 cases), 7 in Southern Europe (2 from Italy [20, 22], 1 from Switzerland [26], 2 from France [10, 25], 1 from former Yugoslavia [11] and 1 from Spain [14], for a total of 4,826 cases), 6 studies came from Asia (5 from Japan [15, 17, 23, 29, 30] and 1 from Singapore/China [12], for a total of 2,020 cases), and 1 from South America (Argentina [24], 190 cases). Ten of the 24 studies (5,371 cases) reported data for men [13, 16, 21, 22, 25, 27–31] and 9 (4,372 cases) for women [13, 16, 21, 22, 27–31] separately.

Statistical analysis

To avoid the exclusion of the studies [8, 23, 28] whose reference category included also drinkers of less than one cup/day (occasional drinkers), our reference category included non-drinkers and occasional drinkers. To compute the summary OR for drinkers versus non/occasional drinkers, when one study reported more than one category of coffee consumption, we first calculated the study-specific pooled estimate for drinkers using the fixed-effects model. We also computed the study-specific pooled estimates to

Table 1 Characteristics of case–control studies of coffee consumption and colorectal, colon, and rectal cancer risk

First author	Country	Years of study	Type of controls	Number of cases	Adjustment factors
Higginson et al. [8][a]	USA	Not indicated	Hospital	340 CRC	
Bjelke et al. [9][b]	Norway	1967–1968	Hospital	169 CC	
Macquart-Moulin et al. [10][b]	France	1979–1984	Hospital	399 CRC	Age, sex, weight, total calories
Jarebinski et al. [11][b]	Yugoslavia	1984–1986	Hospital (50%) Population (50%)	98 RC	Age, sex, residence
Lee et al. [12]	Singapore	1985–1987	Hospital	203 CRC 132 CC 71 RC	Age, sex, dialect, occupation
Rosenberg et al. [13][c]	USA	1978–1986	Hospital	717 CC 313 CC (M) 404 CC (W) 538 RC 267 RC (M) 271 RC (W)	Age, sex, year of interview, education, race, religion, residence, smoking, alcohol
Benito et al. [14][b]	Spain (Majorca)	1984–1988	Population	286 CRC	Age, sex, body weight (10 years before)
Kato et al. [15]	Japan	1986–1990	Population	132 CC 91 RC	Age, sex, residence
Slattery et al.[15]	USA	1979–1983	Population	112 CC (M) 119 CC (W)	Age, body mass index, total calories, fiber, religion
Hoshiyama et al. [17]	Japan	1984–1990	Population	79 CC 102 RC	Age, sex
Olsen et al. [18]	Denmark	1986–1990	Hospital (nested in a randomized trial)	49 CRC	Age, sex, fiber
Baron et al. [19]	Sweden	1986–1988	Population	569 CRC 352 CC 217 RC	Age, sex, body mass index, physical activity, fat, fiber
Centonze et al. [20]	Italy	1987–1989	Population	119 CRC	Age, sex, education, smoking, modification of diet, cereals, diary products, vegetables, fruit, sugar, wine
Shannon et al. [21]	USA	1985–1989	Population	238 CC (M) 186 CC (W)	Age, total energy
Tavani et al. [22]	Italy	1985–1996	Hospital	3,530 CRC 1,176 CC (M) 990 CC (W) 1,364 RC	Age, sex, study, center, education, body mass index, smoking, number of meals, alcohol, meat, vegetables, fruit, total calories
Inoue et al. [23]	Japan	1990–1995	Hospital	362 CC 266 RC	Age, sex, calendar year, season at first hospital visit, smoking, alcohol, physical activity, fruit, rice, beef, tea
Munoz et al. [24]	Argentina	1993–1997	Hospital	190 CRC	Age, sex, social class, body mass index, tea, mate
Boutron-Ruault et al. [25]	France	1985–1990	Population	171 CRC 43 right CC (M) 63 left CC (M) 65 RC	Age, sex, total calories

Table 1 continued

First author	Country	Years of study	Type of controls	Number of cases	Adjustment factors
Levi et al. [26]	Switzerland	1992–1997	Hospital	223 CRC 119 CC 104 RC	Age, sex, education, smoking, alcohol, body mass index, physical activity, total calories
Slattery et al. [27]	USA	1991–1994	Population	1,993 CC 1,089 CC (M) 904 CC (W)	Age, body mass index, physical activity, total calories, sucrose, smoking, alcohol
Woolcott et al. [28]	Canada	1992–1994	Population	969 CC 538 CC (M) 431 CC (W) 857 RC 530 RC (M) 327 RC (W)	Age, sex, education, body mass index, total calories, calcium, fiber, cholesterol, medical condition
Zhang et al. [29]	China	1996–1998	Population	57 CRC (M) 45 CRC (W)	Matched for age, sex, residence. Adjustment factors not reported
Yeh et al. [30]	Taiwan	1995–1999	Hospital	173 CC (M) 159 CC (W) 210 RC (M) 143 RC (W)	For men: age, education, physical activity, smoking, alcohol, meat, vegetables, fruit, fish, shrimp For women: age
Murtaugh et al. [31]	USA	1997–2001	Population	559 RC (M) 393 RC (W)	Age, physical activity, total calories, fiber, calcium

CRC colorectal cancer, *CC* colon cancer, *RC* rectal cancer, *M* men, *W* women

[a] Odds ratio and confidence interval calculated from data

[b] Confidence interval calculated from data

[c] Odds ratio and confidence interval calculated from data for the analyses in which non/occasional drinkers were the reference category

compute the overall colorectal, colon and rectal cancer risk in all subjects in studies where risk estimates in men and women were reported only separately.

To assess the relation of colorectal cancer risk for an increment of one cup of coffee per day, when such estimate was not reported in the original study, we estimated the study-specific OR by relating the natural logarithm of the OR to the corresponding mean value of coffee intake across exposure categories, using the method proposed by Greenland and Longnecker [45, 46], taking into account the fact that estimates of risk for subsequent levels of intake are correlated. Since the highest category of consumption was usually open, we considered it of the same amplitude as the previous category. When the number of subjects in each level was not available, we calculated the dose-risk slopes using the variance-weighted least squares regression. Then we pooled the study-specific estimates by a random-effects model, to obtain the summary OR [47]. To compare the results of our meta-analysis with those of a meta-analysis of prospective cohort studies [5], we also considered the ORs for the highest versus the lowest categories of consumption in each study. In these analyses, the reference category was non/low drinkers, which included non-drinkers or the lowest amount of drinking as classified in each study, independently of the absolute number of drinks/day, and excluding studies where the amount of drinking was not split into two or more categories [24, 29, 30]. Summary measures were calculated using random-effects model that considers both within-study and between-study variations [47]. We also explored the differences by type of controls (population or hospital), sex and geographic regions (North America, Northern Europe, Southern Europe or Asia), given the various sources of heterogeneity and the international differences in coffee consumption.

We presented combined estimates using forest plots. In these graphs, a square was plotted for each study whose centre projection on the underlying scale corresponds to the study-specific OR. The area of the square is proportional to the inverse of the variance of the natural logarithm of the OR, thus giving a measure of the amount of information available from each estimate. A diamond was used to plot the summary OR, the centre of which represents the OR and the extremes show the 95% CIs. We assessed the

statistical heterogeneity among studies using the χ^2 test and quantified the inconsistency using the I^2 statistic [48]; results were defined as heterogeneous for p values <0.10 [49]. There was no evidence of publication bias overall as tested using funnel plots [50] and Begg's and Egger's tests [51]. All the analyses were performed using the Stata® statistical package (version 10; StataCorp, College Station, TX, USA).

Results

Table 2 shows the summary ORs of colorectal, colon and rectal cancer for coffee drinkers versus non/occasional drinkers. The summary ORs were 0.83 (based on 13 studies and 9,568 cases) for colorectal (p for heterogeneity <0.001; $I^2 = 80.0\%$), 0.93 (based on 11 studies and 7,537 cases) for colon (p for heterogeneity <0.001; $I^2 = 81.7\%$), and 0.98 (based on 10 studies and 4,594 cases) for rectal cancer (p for heterogeneity <0.001; $I^2 = 71.2\%$). Table 2 also shows the summary ORs for an increment of one cup of coffee/day, which were 0.94 (95% CI 0.91–0.98) for colorectal (p for heterogeneity <0.001; $I^2 = 69.3\%$), 0.95 (95% CI 0.92–0.98) for colon (p for heterogeneity = 0.002; $I^2 = 60.8\%$), and 0.97 (95% CI 0.95–0.99) for rectal cancer (p for heterogeneity = 0.347; $I^2 = 10.2\%$).

Figure 1 shows the ORs for colorectal, colon, and rectal cancer for each case–control study and the summary OR for the highest category of coffee consumption compared to the lowest one (including non-drinkers and labeled non/low drinkers) as classified in each case–control study, independently of the number of drinks/day, and including only studies splitting coffee drinkers of ≥1 drink/day at least into two categories. Significant heterogeneity was found between the studies included for the summary estimates of OR for colorectal and colon, but not rectal cancer. The summary ORs were 0.70 (95% CI 0.60–0.81) for colorectal cancer (15 studies, Fig. 1a), 0.75 (95% CI 0.64–0.88) for colon cancer (14 studies, Fig. 1b), and 0.87 (95% CI 0.75–1.00) for rectal cancer (12 studies, Fig. 1c).

The same categories of coffee consumption were used in the analyses in strata of geographic area, type of controls, and sex (Table 3). The ORs were 0.76 (95% CI 0.65–0.89) for colorectal, 0.88 (95% CI 0.67–1.16) for colon and 0.96 (95% CI 0.81–1.13) for rectal cancer in North American studies, 0.66 (95% CI 0.41–1.10) for colorectal, 0.55 (95% CI 0.39–0.79) for colon and 0.86 (95% CI 0.43–1.73) for rectal cancer in Northern European studies, 0.72 (95% CI 0.50–1.05) for colorectal, 0.82 (95% CI 0.62–1.10) for colon and 0.96 (95% CI 0.75–1.22) for rectal cancer in Southern European studies, and 0.61 (95% CI 0.50–0.74) for colorectal, 0.60 (95% CI 0.42–0.85; 95% CI 0.45–0.81, respectively) for colon and rectal cancer in Asian studies.

Table 2 Summary odds ratios and 95% confidence intervals of colorectal, colon, and rectal cancer according to coffee drinking

Drinking habit[a]	Colorectal cancer						Colon cancer						Rectal cancer					
	No. of studies	No. of cases	OR	95% CI	P^b	$I^{2\,c}$ (%)	No. of studies	No. of cases	OR	95% CI	P^b	$I^{2\,c}$ (%)	No. of studies	No. of cases	OR	95% CI	P^b	$I^{2\,c}$ (%)
Drinkers	13	9,568	0.83	0.73–0.95	<0.001	80.0	11	7,537	0.93	0.81–1.07	<0.001	81.7	10	4,594	0.98	0.85–1.13	<0.001	71.2
Increment of 1 cup/day	13	9,380	0.94	0.91–0.98	<0.001	69.3	12	7,713	0.95	0.92–0.98	0.002	60.8	10	4,516	0.97	0.95–0.99	0.347	10.2

OR odds ratio, *CI* confidence interval

[a] Reference category was non/occasional drinkers

[b] *P* for heterogeneity among studies

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

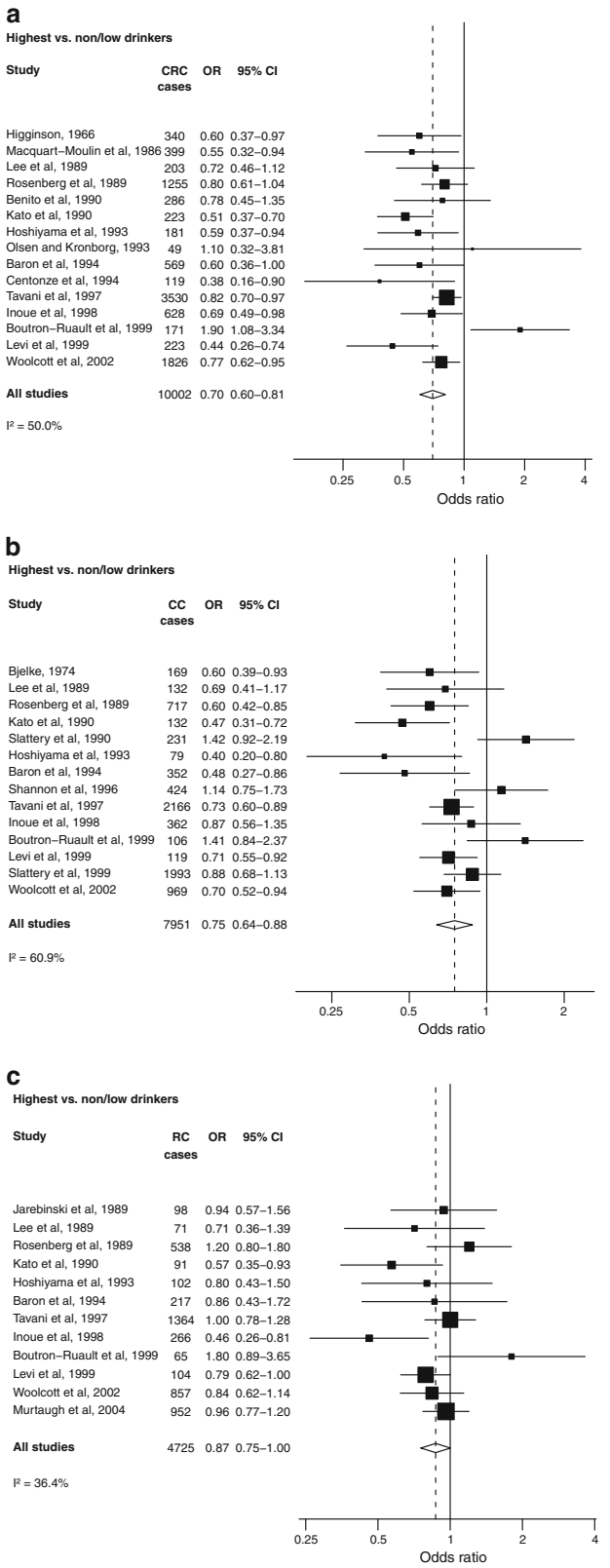

Fig. 1 Forest plots of studies of the risk of colorectal cancer (CRC) (**a**), colon cancer (CC) (**b**) and rectal cancer (RC) (**c**) for highest versus non/low coffee drinkers

Analysis in strata of type of controls gave similar results, with summary ORs of 0.71 (95% CI 0.52–0.88) and 0.73 (95% CI 0.64–0.83), respectively, for population and hospital controls for colorectal cancer; the corresponding ORs were 0.80 (95% CI 0.59–1.07) and 0.70 (95% CI 0.62–0.80) for colon, and 0.88 (95% CI 0.72–1.07) and 0.87 (95% CI 0.69–1.10) for rectal cancer. The summary ORs for colorectal cancer were 0.76 (95% CI 0.61–0.94) in women (based on 2 studies and 1,433 cases) and 1.17 (95% CI 0.66–2.05) in men (based on 3 studies and 1,757 cases). The corresponding values were, for colon cancer, 0.79 (95% CI 0.63–0.99) in women (based on 6 studies and 3,034 cases) and 0.90 (95% CI 0.66–1.21) in men (based on 6 studies and 3,466 cases), and, for rectal cancer, 0.90 (95% CI 0.71–1.13) in women (based on 3 studies and 991 cases) and 1.05 (95% CI 0.83–1.33) in men (based on 3 studies and 1,356 cases). Although the inverse association was apparently stronger or restricted to women, the test for heterogeneity between the ORs in women and men was not significant for colorectal cancer or for each site separately.

The pooled estimate of the effect of the highest level of consumption versus non/low drinkers on the risk of colorectal cancer by calendar year of publication is shown in Fig. 2. The cumulative OR was about 0.6 for studies published up to 1994 and between 0.67 and 0.69 for more recent studies, all statistically significant.

Discussion

This meta-analysis of case–control studies found that the risk of colorectal cancer for regular coffee drinkers was approximately 17% lower than for non/occasional drinkers. The protection was about 30% for the highest coffee drinkers and 6% for an increase in consumption of one cup of coffee/day. The inverse association was stronger for colon than for rectal cancer. The apparently lower pooled OR for colorectal than that of colon or rectal cancer reflects differences in the composition of studies used to estimate the relation of coffee drinking with cancer at various anatomical sites. The same was true for the separate estimates in men and women and that including both sexes.

A meta-analysis of data collected before June 1997 [4] found a cumulative RR of colorectal cancer of 0.97 (95% CI: 0.73–1.29) for cohort studies and 0.72 (95% CI: 0.61–0.84) for case–control studies for high versus low categories of coffee consumption. Thus, our findings confirm the previous ones of case–control studies. In the present analysis, the inverse relation was also consistently observed in populations with different baseline colorectal cancer incidences and different patterns of coffee

Table 3 Summary odds ratios and 95% confidence intervals of colorectal, colon, and rectal cancer for highest versus non/low drinkers of coffee in strata of according geographic area, type of controls, and sex

	Colorectal cancer						Colon cancer						Rectal cancer					
	No. of studies	No. of cases	OR	95% CI	P^a	$I^{2\,b}$ (%)	No. of studies	No. of cases	OR	95% CI	P^a	$I^{2\,b}$ (%)	No. of studies	No. of cases	OR	95% CI	P^a	$I^{2\,b}$ (%)
Geographic area[c]																		
North America	3	3,421	0.76	0.65–0.89	0.576	0.0	5	4,334	0.88	0.67–1.16	0.011	69.1	3	2,347	0.96	0.81–1.13	0.386	0.0
Northern Europe	2	618	0.66	0.41–1.10	0.376	0.0	2	521	0.55	0.39–0.79	0.548	0.0	1	217	0.86	0.43–1.73	–	–
Southern Europe	6	4,728	0.72	0.50–1.05	0.002	73.5	3	2,391	0.82	0.62–1.10	0.053	66.2	4	1,631	0.96	0.75–1.22	0.140	45.2
Asia	4	1,235	0.61	0.50–0.74	0.525	0.0	4	705	0.60	0.42–0.85	0.132	46.5	4	530	0.60	0.45–0.81	0.587	0.0
Type of controls																		
Population	7	3,375	0.71	0.52–0.88	0.003	69.3	8	4,286	0.80	0.59–1.07	<0.001	75.3	7[d]	2,382[d]	0.88	0.72–1.07	0.256	22.7
Hospital	8	6,627	0.73	0.64–0.83	0.325	13.4	6	3,665	0.70	0.62–0.80	0.798	0.0	6[d]	2,441[d]	0.87	0.69–1.10	0.074	50.2
Sex																		
Men	3	1,757	1.17	0.66–2.05	0.009	78.7	6	3,466	0.90	0.66–1.21	0.013	65.4	3	1,356	1.05	0.83–1.33	0.450	0.0
Women	2	1,433	0.76	0.61–0.94	0.530	0.0	6	3,034	0.79	0.63–0.99	0.104	45.3	3	991	0.90	0.71–1.13	0.677	0.0

OR odds ratio, *CI* confidence interval

[a] *P* of heterogeneity between studies

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

[c] North America included USA (6 studies) and Canada (1 study); Northern Europe included Norway (1 study), Denmark (1 study), and Sweden (1 study); Southern Europe included Italy (2 studies), Switzerland (1 study), France (2 studies), Yugoslavia (1 study), and Spain (1 study); Asia included Japan (3 studies) and China (Singapore, 1 study). South America is not included in the analysis as Munoz et al. [24] reported data only for drinkers versus non-drinkers

[d] The sum of the number of studies and cases does not add up to the total because Jarebinski et al. [11] include both population and hospital controls

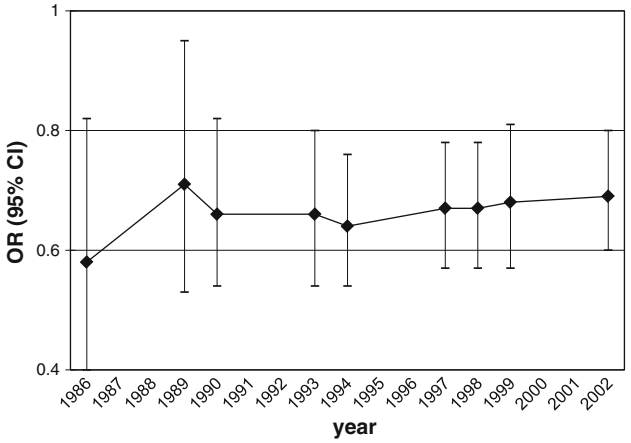

Fig. 2 Cumulative ORs of the effect of the highest versus non/low coffee drinkers on the risk of colorectal cancer by calendar year of study publication

consumption. A recent meta-analysis of cohort studies based on 12 studies and including 5,403 cases of colorectal cancer found a RR of 0.91 (95% CI: 0.81–1.02) of borderline significance, comparing high to low categories of coffee consumption [5], and a pooled analysis of 13 prospective studies found no association overall and in strata of anatomical site of cancer, sex, smoking, alcohol, body mass index, and physical activity [6]. However, a Chinese prospective study published after the meta- and pooled analysis found an overall RR of 0.89 (95% CI 0.66–1.19) in drinkers of two or more coffee per day and of 0.56 (95% CI 0.35–0.90) in ever smokers [7].

Therefore, there are still differences between results of cohort and case–control studies of coffee and colorectal cancer risk. The discrepancy may partly by be related to the different time-exposure considered, closer to cancer incidence in case–control studies. This is supported by the finding that cohort studies with a follow-up shorter than 10 years are more likely to show an inverse association between coffee intake and colorectal cancer risk than studies with longer follow-up [5].

The consistency of results from case–control studies over calendar years indicates that the inverse association between coffee drinking and colorectal cancer risk is unlikely to be a false positive finding due to selective reporting of earlier studies [52], as the cumulative OR for recent studies, in general larger and more accurately adjusted for potential confounding factors, was only 5–9% higher and, given the interest in the issue, also null results have been published, thus limiting the scope for publication bias. In addition, the finding of a dose-risk relation further supports the real inverse association. However, the categories of low and the high drinkers varied across the studies included in this meta-analysis, as coffee drinking is more frequent in North America and Northern Europe than in Southern Europe and even less common in Asia. Consequently, the overall estimates for high drinkers were based on study-specific definitions and can only be considered indicative of an inverse dose-risk relation.

We cannot exclude some misclassification in colorectal cancer diagnosis. However, most studies included in the meta-analysis reported that cases of colorectal cancer were histologically confirmed, and diagnosis and certification of all intestinal sites, including colon and rectum, have long been sufficiently reliable, and have not substantially changed over the last decades. The distinction between colon and rectum cancer poses some problems (since a large proportion of cancers arise in the recto-sigmoid junction) [53], which should not, however, have affected our estimates based on all intestinal cancers combined and might have weakened the cumulative estimate for colon cancer risk, if the association is stronger for colon than for rectum. Thus, it is unlikely that problems in diagnosis and certification practices may have meaningfully affected the overall risk estimates.

Subjects with digestive tract disease, such as inflammatory bowel disease (a risk factor for colorectal cancer), may avoid coffee because of side effects of coffee or following non-specific medical advice (reverse causation) [54]. However, several possible mechanisms support a real inverse association of coffee intake with colorectal (mainly colon) cancer risk [55]. Coffee contains several antioxidant and antimutagenic compounds with potential anticarcinogenic effects in animal models and cell culture systems [56], whose concentrations in the beverage vary depending on the type of raw coffee (Arabica or robusta), roasting, and preparation [57]. They include phenolic compounds (such as chlorogenic, caffeic, ferulic, and cumaric acids) [58], melanoidins and diterpenes (such as cafestol and kahweol). In particular, cafestol and kahweol reduce the oxidant effect of polycyclic aromatic hydrocarbons and several other carcinogens. Specific possible mechanisms in the colon include the reduction in bile acid secretion (a promoter of colon cancer) [59], reduction in synthesis by down-regulation of the expression of bile acid homeostatic genes [60], an increase in colonic motility (mainly at the rectosigmoid junction and in women) [61]. Patients with type-2 diabetes are at increased risk of colon cancer [62–64]. Coffee has antidiabetic properties [65], and the chlorogenic acid contained in coffee reduces glucose absorption in the intestine [66]. A lower concentration of C-peptide (a marker of insulin secretion) [67] was found in women drinking more than 4 cups/day [68], and a prospective study from New York State observed a threefold higher risk of colorectal and colon cancer in women in the top quartile of C-peptide [69].

We observed an apparently stronger inverse relation in women, although the difference was not significant. If real,

this can be partly related to sex hormones that have also been associated to reduced colorectal cancer risk [70, 71], and caffeine has been related to sex-hormone-binding globulins [72]. However, the issue remains open to discussion.

Observational studies included in this meta-analysis may have various sources of bias and confounding. Selection and report bias might have operated in case–control studies; however, the consistency of results between type of controls (population and hospital), geographic regions and participation rate, that was satisfactory in most studies, argues against it. Furthermore, the different coffee consumption measurements and the consequent arbitrary classification of consumption may explain the heterogeneity among studies. Moreover, most studies included did not mention type of coffee power, brewing methods, preparation, and cup size, which may modify the relation, since for example boiled (unfiltered) coffee contains smaller amounts of the lipid components of coffee (diterpenes, such as cafestol and kahweol) with anticarcinogenic activities [73]. An important difficulty concerned the assessment of coffee intake based on patients' self-reporting. However, recall of coffee drinking has been shown to be satisfactorily reproducible and valid [74, 75] and should not be different on the basis of the disease status or among various types of controls, as coffee is not commonly known to affect colorectal cancer risk. A few early studies did not adjust for relevant confounding factors, such as smoking, body mass index, or physical activity. This may be partly responsible for heterogeneity among studies.

However, the exclusion of each single study did not change the summary estimate, and although we did not search for unpublished data or abstracts, given the difficulties in their interpretation, no significant asymmetry was seen in the funnel plot, indicating that publication bias is unlikely to have materially influenced the results.

We were unable to consider the relation between caffeine and the risk of colorectal cancer because most published studies reported only the number of cups of coffee consumed, with no information on caffeine intake. Although caffeine intake depends on the variety of raw coffee and the preparation method, and it is also found in cola, energy drinks and several drugs, coffee drinking is its major source and is strongly correlated with total caffeine intake in Europe and North America [1].

In conclusion, this systematic meta-analysis of case–control studies provides quantitative evidence of an inverse relation between coffee drinking and colorectal (mainly colon) cancer risk. Although bias and confounding were unlikely responsible for the consistent results in different countries, settings and time, the interpretation of this association in terms of causality remains open to discussion, also considering the lack of information on the relation with duration and other time-related factors, and the quantitative difference in the estimates from case–control and cohort studies [5].

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Conflict of interest None.

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