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Meta-analysis of Coffee Consumption and Risk of Colorectal Cancer

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Several studies have found that coffee consumption is related to a lower risk of colorectal cancer, but results have not been consistent. Thus, a meta-analysis of the published articles was conducted to examine this relation. Because of the various ways data were collected and analyzed, a "semiquantitative" approach that compared the high versus the low category of intake for each study was used. The combined results from 12 case-control studies showed an inverse association between coffee consumption and risk of colorectal cancer (pooled relative risk (estimated by odds ratio) for high vs. low category of coffee consumption (RR) = 0.72, 95% confidence interval (CI) 0.61–0.84); the findings were similar in population-based and hospital-based case-control studies. Five cohort studies did not support an association (pooled RR = 0.97, 95% CI 0.73–1.29). The combined results of all studies were driven largely by the case-control studies, which comprised 85 percent of the cases (RR = 0.76, 95% CI 0.66–0.89). The lower risk of colorectal cancer among substantial coffee drinkers was observed in studies from Asia, Northern and Southern Europe, and North America. The results of this meta-analysis indicate a lower risk of colorectal cancer associated with substantial consumption of coffee, but they are inconclusive because of inconsistencies between case-control and prospective studies, the lack of control for important covariates in many of the studies, and the possibility that individuals at high risk of colorectal cancer avoid coffee consumption. Several ongoing prospective cohort studies, based on extensive dietary questionnaires, may provide important new data to evaluate this hypothesis. *Am J Epidemiol* 1998;147:1043–52.

caffeine; coffee; colorectal neoplasms; meta-analysis

Studies have often found a lower risk of large bowel cancer associated with higher coffee consumption, although this finding has not been universal (1). Coffee's composition is quite complex, and varied constituents have potential genotoxic, mutagenic, and antimutagenic properties (2). In addition, coffee modulates various physiologic processes, such as large bowel motility (3), that could alter colonic exposure to potential fecal carcinogens. Given widespread consumption of coffee and the high incidence of colorectal cancer in developed countries, any relation between these would have appreciable public health relevance. Thus, the literature was reviewed and a meta-analysis was conducted to estimate the magnitude of any association between coffee consumption and colorectal cancer risk. The association was further examined by anatomic site (total colorectal, colon, and rectum), study design (cohort and hospital-based and population-based case-control studies), and geographic region or country of the study population.

MATERIALS AND METHODS

Literature review for meta-analysis

The MEDLINE and CANCERLIT databases were searched through June 1997, and references in all articles were cross-checked to obtain all pertinent publications on coffee consumption and risk of colorectal cancer. As minimal criteria, the studies adjusted risk estimates for age and sex and provided quantification of risk including confidence intervals. If confidence intervals were not provided, but numbers of cases and controls in high versus low categories of coffee consumption were, these data were used to estimate confidence intervals. Twelve case-control studies meeting these criteria were identified (table 1) (4–15), dividing evenly into those using other hospital patients as controls and those relying on random sampling of the population at risk. Only five cohort studies met the criteria for inclusion (table 2) (16–20). A description of the results from identified studies not used in the meta-analysis is given in Results.

For the meta-analysis, studies were classified as cohort or prospective, in which individuals catego-

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Abbreviations: CI, confidence interval; RR, relative risk.

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TABLE 1. Summary of case-control studies of coffee consumption and colorectal cancer

First author, year of publication	Years of study	Type of controls	Study population		Coffee ("high" vs. "low")*	Odds ratio†	Adjusted for
			Geographic location	No. of cases			
Bjelke, 1974	1967–1968	Hospital based	Norway	162	≥5 cups/day vs. <3 cups/day	0.6 (0.39–0.93)‡,§	Age, sex
Tuyns, 1988	1978–1982	Population based	Belgium	453 (C) 365 (R)	Top vs. bottom quartile	0.62 (0.43–0.90) 0.68 (0.45–1.02)	Age, sex, province
Macquart-Moulin, 1986	1979–1984	Hospital based	France	399	Top vs. bottom quartile	0.55 (0.32–0.94)	Age, calories, body weight
Lee, 1989	1985–1987	Hospital based	China	203 132 (C) 71 (R)	"High" vs. "low"	0.74 (0.46–1.17) 0.69 (0.41–1.17) (C) 0.71 (0.36–1.38) (R)	Age, sex, vegetables, meats, cholecystectomy
Kato, 1990	1986–1990	Population based	Japan	221	Daily vs. less than daily	0.47 (0.31–0.72) (C) 0.57 (0.35–0.93) (R)	Age, sex, region
Centonze, 1994	1987–1989	Population based	Southern Italy	119	>2 cups/day vs. none	0.38 (0.16–0.89)	Age, sex, smoking, various dietary factors
Baron, 1994	1986–1988	Population based	Sweden	352 (C) 217 (R)	>5 cups/day vs. <1 cup/day	0.48 (0.27–0.86) (C) 0.86 (0.43–1.73) (R) 0.60 (0.36–1.00)	Age, sex, smoking, fat, fiber, body mass, exercise
Benito, 1990	1984–1988	Population based	Majorca, Spain	286	"High" vs. "low"	0.78 (0.45–1.35)§	Age, sex, body weight
Rosenberg, 1989	1978–1986	Hospital based	United States	717 (C) 538 (R)	≥5 cups/day vs. <1 cup/day	0.6 (0.4–0.8) (C) 1.2 (0.8–1.8) (R)	Age, sex, region, cigarettes, alcohol, education, religion, race
Bidoli, 1992	1986–1990	Hospital based	Northeastern Italy	123 (C) 125 (R)	"High" vs. "low"	1.0 (0.61–1.65)§ (C) 1.1 (0.69–1.75)§ (R)	Age, sex, social status
Slattery, 1990	1979–1983	Population based	Utah (United States)	112 (C)♂ 119 (C)♀	≥2.5 cups/day (approximately) vs. none	2.2 (1.20–4.00)♂ 0.9 (0.50–1.70)♀	Age
La Vecchia, 1989	1983–1988	Hospital based	Northern Italy	455 (C) 295 (R)	≥3 cups/day vs. none	0.59 (0.43–0.80)§ (C) 0.66 (0.46–0.95)§ (R)	Age, sex, social class, education, martial status, smoking, alcohol

* One cup = 237 ml.
† Note: odds ratios for total colorectal cancers unless specified for colon (C) or rectum (R).
‡ Numbers in parentheses, 95% confidence interval.
§ Standard error calculated from data.

TABLE 2. Summary of cohort studies of coffee consumption and colorectal cancer

First author, year of publication	Years of follow-up	Study population: Geographic location	Study population: No. of cases	Coffee ("high" vs. "low")*	Relative risk†	Adjusted for
Wu, 1987	1982–1985	United States (retirement community	58 ♂ 68 ♀	≥4 cups/day vs. ≤1 cup/day	1.54 (0.7–2.7)‡ ♂ 1.17 (0.4–3.1) ♀	Age
Klatsky, 1988	1978–1984	United States	203 (C) 66 (R)	Continuous variable (cups/day)	0.92 (0.80–1.06) (C) 0.84 (0.66–1.07) (R)	Age, sex, alcohol, smoking, race, body mass, cholesterol, education
Jacobson, 1986	1967–1978	Norway	100 (C) 63 (R)	≥7 cups/day vs. ≤ 2 cups/day	0.54 (0.22–1.30)§ (C) 1.07 (0.41–2.78)§ (R)	Age, sex, residence, alcohol
Stensvold, 1994	1977–1990	Norway	78 (C) ♂ 52 (C) ♀ 41 (R) ♂ 48 (R) ♀	Continuous variable (cups/day)	0.98 (0.81–1.19) (C) ♂ 0.96 (0.74–1.25) (C) ♀ 0.92 (0.71–1.20) (R) ♂ 0.86 (0.63–1.17) (R) ♀	Age, sex, region, county
Phillips, 1985	1960–1980	United States (Seventh-day Adventists)	53 (C) ♂ 83 (C) ♀ 28 (R) 164 (C and R)	≥2 cups/day vs. <1 cup/day (C) ≥1 cup/day vs. <1 cup/day (R)	2.0 (1.1–3.6) (C) ♂ 1.5 (0.8–2.6) (C) ♀ 1.4 (0.6–3.1) (R) 1.5 (1.6–2.2) (C and R)	Age, sex

* One cup = 237 ml.
† Note: relative risks for total colorectal cancers unless specified for colon (C) or rectum (R).
‡ Numbers in parentheses, 95% confidence interval.
§ Standard error calculated from data.

rized by coffee consumption level were followed for cancer occurrence, and as case-control, in which colorectal cancer cases and controls free from this malignancy were identified, and information on coffee consumption prior to diagnosis for cases was obtained and compared with that over a similar time period for controls. Case-control studies were further divided into population based (where the comparison group was identified from the catchment population from which the cases arose) and hospital based (where the comparison group was identified from among other patients at institutions where cases were diagnosed). Three studies examining coffee intake in relation to incidence of colorectal adenomas (4, 21, 22), precursors of cancer (23), were also identified.

Data extraction and classification

Generally, coffee consumption was part of a broader assessment, and the relation between coffee consumption and colorectal cancer had not been a prior hypothesis. Virtually all studies reported relative risks of colorectal cancer by categories of coffee consumption. For example, cancer incidence for each level of coffee consumption of 1–2, 3–4, and ≥5 cups per day (1 cup = 237 ml) was compared relative to the incidence among nondrinkers. Several studies reported a relative risk for a unit increase in coffee consumption (18, 19). If the risk of colorectal cancer was expressed in more than one way, the estimate reflecting the greatest degree of controlling for confounders was used.

A common approach to quantify risk in a meta-analysis is to calculate from each study a coefficient for relative risk based on coffee consumption as a continuous variable, which would allow a unit change in relative risk (on the natural logarithm scale) per each cup of coffee. However, several major theoretical and practical considerations prevented the use of this methodology. This approach entails arbitrarily assigning values to categories of coffee consumption, including the upper open-ended category of consumption (e.g., ≥5 cups/day). Even more problematic, five of the 12 case-control studies reported data only for ordered categories (e.g., tertiles or quartiles) but did not quantify consumption level. Beyond the assumptions necessary to assign values, several of the largest studies (12, 14) did not display clear evidence of a monotonic dose-response relation. Finally, preparation methods of coffee as well as cup size vary substantially across countries, and the caffeine content per cup varies from 19 to 160 mg according to type of coffee, cup size, and country (24).

Because of these limitations, a more conservative "semiquantitative" approach was used. Instead of possibly mis-specifying a dose-response relation, only the high versus low categories of consumption from various studies were examined. This strategy, used by others (25), allows for the inclusion of five of 12 case-control studies providing only categorical data (e.g., relative risk for high vs. low tertiles of coffee consumption). Of 13 studies of cancer and adenoma that provided values for the upper and lower categories, the mean and median of the upper bound were approximately 4 cups per day; usually, the cutoff for the lower category was less than 1 cup per day or zero. For two studies that presented relative risks only as a continuous variable (increment risk on a per cup basis), the relative risk and confidence intervals for a 4-cup increment were calculated.

Statistical methods and analysis

To pool relative risks from several studies, the meta-analytic method relies on a weighted average of the log relative risks from the individual studies. Under the rare disease assumption, odds ratios were used to estimate relative risks in case-control studies. The weight depends on the inverse of the variance of the log relative risk, giving larger studies greater weight in the summary measure (26). A random effects method that does not assume homogeneity of relative risks (i.e., uniformity of the association) across studies was used (27). This method is conservative and produces a relatively larger variance (and hence wider confidence intervals) than methods that assume homogeneity of risk. In this analysis, various sources of heterogeneity are likely. For example, results are combined from different countries, and there are international differences in typical volume of coffee consumed, coffee type, or brewing method and the underlying risk of colorectal cancer.

To convert confidence intervals from the different studies into estimates of the variance of the log relative risk, the interval was transformed to the log scale. Under the assumption that the 95 percent confidence interval had been constructed by adding and subtracting 1.96 times the standard error of the log relative risk, interval length (upper minus lower bound) is divided by 3.92 to obtain an approximate standard error, which was then squared to estimate the variance. When only a relative risk and numbers of cases and controls in the high and low coffee categories were provided, the crude numbers were used to calculate a standard error of the crude odds ratio. This standard error was then used to approximate confidence intervals for the reported adjusted odds ratio.

RESULTS

Overall results of meta-analysis

The results from the individual studies are shown in tables 1 and 2. In all studies combined, substantial coffee drinkers had a 24 percent lower risk of colorectal cancer relative to infrequent drinkers or nondrinkers (table 3). This inverse association was primarily due to the 12 case-control studies, which contributed 85 percent of total cases. The relative risk (estimated by the odds ratio) was similar for population-based and hospital-based studies. The five cohort studies, which contributed many fewer cases, did not show a relation. Because most cases were from case-control studies, the relative risk from the total studies (RR = 0.76) differed only slightly from that of the case-control studies (RR = 0.72). Of all 10 countries (United States, Norway, Belgium, Denmark, Sweden, France, Italy, Spain, China, and Japan) that provided some data, including studies not in the meta-analysis, at least one study from each country found evidence of a lower colorectal cancer risk with higher coffee consumption (table 4). In three adenoma studies, a 43 percent reduction in risk was associated with higher coffee consumption.

Case-control studies

As summarized in table 1, 10 of the 12 case-control studies found a lower risk among substantial coffee consumers. In nine of these, the relative risk associated with higher coffee intake ranged between 0.4 and 0.7, and most were in the range of 0.6. In seven case-control studies that presented results separately for colon and rectum, the relative risks were nearly identical for the colon (RR = 0.81) and rectum (RR = 0.80). The published studies did not present results separately for the proximal and distal colon; thus, although there is evidence (28) of differences in the carcinogenesis of proximal and distal colon cancer, differences regarding the role of coffee could not be evaluated.

Seven reports from case-control studies could not be included in the meta-analysis, because results were not quantified or because all sources of caffeine were combined. A hospital-based case-control study of Hawaiian Japanese reported a relative risk of 0.72 for coffee consumption "above average" compared with "below average" (29). An abstract published in 1981 by Abu-Zeid et al. (30) reported among Canadians "a low risk" for coffee drinkers, but the risks were not quantified, and no confidence intervals were given. Several case-control studies have reported "no association" with coffee (31, 32), or a slight positive association (33), but without offering any quantification of risk. One case-control study found no association with caffeine but did not report findings specifically for coffee (34). Finally, a case-control study found no appreciable association with colorectal cancer, although a slight inverse association (RR = 0.8) with higher consumption of caffeine-containing beverages was noted for rectal cancer among women (35); however, this study combined "tea, coffee, cola, etc." so the specific effect of coffee could not be evaluated.

Cohort studies

The cohort or prospective studies were less supportive of an association than the case-control studies (tables 2 and 3). Some of these studies were based on

TABLE 4. Relative risk (RR) or odds ratio (OR) and 95% confidence interval of colorectal cancer for "high" versus "low" coffee consumption from meta-analysis, by geographic location of study*

	No. of studies	No. of colorectal cancer cases	RR or OR	p value
Northern Europe	5	1,921	0.65 (0.53–0.79)†	<0.001
Southern Europe	5	1,802	0.71 (0.57–0.89)	0.003
United States	3	1,650	0.87 (0.59–1.29)	0.49
Asia	2	424	0.57 (0.44–0.75)	<0.001
Special populations	2	395	1.45 (0.93–2.26)	0.10

* Northern Europe includes Norway, Sweden, and Belgium; Southern Europe includes Italy, France, and Spain; Asia includes Japan and China; and special populations include Seventh-day Adventists and Latter-day Saints, both in the United States.

† Numbers in parentheses, 95% confidence interval.

TABLE 3. Relative risk (RR) or odds ratio (OR) and 95% confidence interval of colorectal cancer for "high" versus "low" coffee consumption from meta-analysis, by study design

	No. of studies	No. of cases	RR or OR	p value
All colorectal cancer studies	17	6,192	0.76 (0.66–0.89)*	<0.001
Cohort studies	5	931	0.97 (0.73–1.29)	0.83
Case-control studies (total)	12	5,261	0.72 (0.61–0.84)	<0.001
Case-control studies (population based)	6	2,244	0.70 (0.53–0.92)	0.01
Case-control studies (hospital based)	6	3,017	0.74 (0.61–0.90)	0.002
Adenoma studies	3	883	0.57 (0.44–0.72)	<0.001

* Numbers in parentheses, 95% confidence interval.

a single measurement of coffee intake and had long follow-up periods of 10 (20), 14 (18), and 21 (17) years. A study of Seventh-day Adventists suggested a positive association between coffee intake and colon cancer risk (17). If this study was excluded from the meta-analysis, the pooled relative risk is 0.84 (with 95 percent confidence interval (CI) 0.62–1.14) for prospective studies.

Several studies reporting findings regarding coffee and colorectal cancer risk were not included in the meta-analysis because relative risk and standard error were not provided. A 14-year follow-up study in Sweden found that coffee was the only food item associated with a lower risk of colon cancer, but no quantification of risk was reported (36). An 18-year follow-up study of 5,249 men in Denmark found a smaller proportion of coffee drinkers of >5 cups/day among 51 men who developed colon cancer (31.4 percent) compared with the men who did not develop this disease (40.1 percent) (21). No association was seen based on 42 rectal cancer cases. The results were not age adjusted. A prospective study based on a single 24-hour recall and up to 18 years of follow-up suggested an inverse trend with coffee consumption and cancer of the rectum ($n = 60$; p, trend, = 0.13) but no association with colon cancer ($n = 108$; p, trend, = 0.98) (37). It is unclear how well a single 24-hour recall can characterize exposure for 18 years of follow-up. Overall, results from prospective studies unusable for the meta-analysis are consistent with an inverse association with colorectal cancer, but they are inconclusive.

Sex-specific analysis

Because sex-specific relative risks were presented in only a small proportion of studies, a meta-analysis by sex was not conducted. The limited data presented did not suggest a strong sex difference. The largest study (14) found a slightly stronger association among women (RR = 0.5) than men (RR = 0.7). The third largest study (10) found almost identical associations in the colon (men, RR = 0.61; women, RR = 0.63), but in the rectum, the association was evident only for men (RR = 0.50 for males and RR = 0.92 for females). One study reported no significant interaction by sex (7), and another reported that the association was broadly similar in men and women (15). One study found a slightly stronger inverse association in women (18), but this report was based on small numbers. All other studies reported sex-adjusted but not sex-specific associations. None reported any substantial differences by sex.

Studies of adenomas

Colorectal adenomas are well-established precursors of cancer (23). A study in Denmark comparing coffee intake among individuals found to have adenomas at colonoscopy relative to those who were free of adenomas found a lower risk with increasing level of coffee consumption (age, sex, fiber-adjusted RR = 0.3; 95 percent CI 0.1–0.5; for ≥8 relative to ≤3 cups of coffee per day) (21). In Japanese male self-defense officials undergoing screening sigmoidoscopy, an inverse association was found between coffee consumption and risk of sigmoid adenoma (RR = 0.61, 95 percent CI 0.33–1.24; for ≥5 cups/day vs. 0 cups; adjusting for smoking, alcohol, body mass index, rice, meats, tea) (22). Another study in Japan comparing individuals with adenomas with population-based controls found an inverse association between coffee consumption and proximal adenomas (age-, sex-, and region-adjusted RR = 0.50, 95 percent CI 0.3–0.84), distal adenomas (RR = 0.6, 95 percent CI 0.4–0.89), and rectal adenomas (RR = 0.72, 95 percent CI 0.40–1.30) for daily coffee drinkers compared with nondrinkers (4). Overall, the three studies that have examined the relation between coffee consumption and the risk of colorectal adenoma found that frequent consumers had approximately half the risk of infrequent consumers (table 3).

DISCUSSION

The results from this meta-analysis indicate that a lower risk of colorectal cancer is associated with higher levels of coffee consumption. This inverse association was remarkably consistent across numerous studies and observed in at least one study in each of 10 different nations. This relation was largely limited to case-control studies, and the evidence from prospective studies was inconclusive. Even though nonsignificant results may be less likely to be published (publication bias), the likelihood that these findings are due to chance alone is remote. In most studies, coffee was not of prime interest but was one of multiple exposures considered and reported. If coffee consumption is unrelated to colorectal cancer, one would expect, through chance, as many studies to have a direct as to show an inverse association. Because of limitations in reported data, the relative risk could not be quantitated rigorously on a per cup basis, but a "semiquantitative" analysis suggests that individuals drinking approximately 4 or more cups of coffee per day had a 24 percent lower risk of colorectal cancer relative to those who rarely or never drink coffee.

The nature of this inverse association is unclear. In case-control studies, selection bias could occur if cof-

fee consumption among the participating controls differs from that in the target population. Some consistent selection bias related to study design accounting for the lower risk of colorectal cancer appears unlikely, because the relation existed in hospital-based and population-based case-control studies, and any mechanism of selection bias is likely to be quite different using these two sources of controls. Reporting bias, such as underreporting by cases, is also a possibility, but the similar associations in such a variety of settings argue against this. Moreover, an association between coffee consumption and lower risk of colorectal cancer was not anticipated or hypothesized when the studies were carried out. Additional prospective data would be useful in excluding these biases.

The published studies, to varying degrees, controlled for factors, such as diet, believed to be related to colorectal cancer. Controlling for a variety of these factors (tables 1 and 2) did not change the results substantially in any study. The consistency of this finding in 10 countries within Northern Europe, Southern Europe, and Asia, as well as the United States, to a lesser degree, argues against residual confounding because it is unlikely that the same confounding factors would be operative in these diverse settings. Moreover, heavy coffee consumption tends to be associated with smoking, alcohol, physical inactivity (18), and possibly higher fat and cholesterol intake (38) that, if anything, enhance the risk of colon cancer.

Of note, the only two studies that provided evidence of a positive association between coffee consumption and the risk of colorectal cancer were from two special populations based on religious denomination (Seventh-day Adventists and Latter-day Saints) (5, 17). In these two studies, even less than 2 cups of coffee per day were associated with an increased risk. That the modest consumption of coffee (e.g., less than 2 cups per day) in these populations substantially increases the risk of colorectal cancer is inconsistent with the inverse association seen with much higher levels in the other studies. Authors of both studies suggest that coffee drinkers in these populations may not adhere to the precepts or norms of these churches (low intake of meats, avoidance of alcohol, and smoking) and thus may differ from other church members in a variety of ways. Thus, confounding probably accounts for the positive associations in these religion-based populations, for whom the connection between coffee and "unhealthy" behaviors is probably much stronger than in other populations.

Another possible explanation for the results is that individuals at high risk for developing colorectal cancer, or who have symptoms from undiagnosed cancer of the large bowel, avoid coffee consumption, though some evidence is contrary. Rosenberg et al. (14) found similar results whether coffee consumption of the prior year or of 3 years previously was analyzed. In a study of coffee consumption and digestive tract cancers (10), higher coffee consumption was associated with a lower rate of cancers of the large bowel, but not for other digestive tract cancers, for which a similar bias could occur. In addition, a prospective study with 14 years of follow-up after the assessment of coffee found an inverse association (36). Finally, studies suggest an inverse association between coffee consumption and the risk of colorectal adenomas, which are largely asymptomatic (39, 40).

Another possibility is that some constitutional risk factors lead to both avoidance of coffee and to a higher risk of colorectal cancer. For example, one survey indicated that 17 of 65 (29 percent) patients with irritable bowel syndrome, a complex disorder of large bowel motility, reported that coffee aggravated their symptoms (3). While the relation between bowel motility and colon cancer is not established, certain disorders of colonic motility may theoretically predispose to both cancer and to avoidance of coffee. On the other hand, the influence of coffee on colonic function is to increase rectosigmoid motility and the desire to defecate (3); if anything, these characteristics may lower cancer risk by reducing colorectal exposure to fecal carcinogens.

Vineis (41) has hypothesized that the apparently protective effect of coffee consumption is not causal, but that slow *N*-acetylators, who may be at lower risk for colorectal cancer, drink more coffee than do fast acetylators (41). Studies have found an excess of rapid acetylators in patients with colon cancer (42, 43) or adenoma (44), though two other studies did not support this (45, 46). *N*-Acetyltransferase is crucial in the metabolism of caffeine, and the neurologic effects of caffeine metabolites could influence coffee consumption, though this is not proven. The magnitude of any association between acetylation rate and coffee consumption would have to be quite strong to entirely account for the results.

Studies have generally relied on a single estimate of general coffee consumption. While coffee consumption over the prior year assessed as cups per day is reasonably well measured (e.g., correlation of 0.82 between a questionnaire and detailed diet records in one study (38)), variances of container size and brewing method, which could influence levels of potentially relevant factors, will add to misclassification (47). Another source of misclassification is the use of a single measure to reflect long-term consumption, which is most likely relevant.

While the possibility that bias or uncontrolled con-

founding accounts for the generally lower risk of colorectal cancer among substantial coffee consumers cannot be excluded, at least three possible causal mechanisms are worth discussing, although other mechanisms are possible.

First, antimutagenic properties of coffee lower risk of colorectal cancer. Coffee and caffeine are able to inhibit the mutagenic effect of numerous factors in various strains of microorganisms (2). The antimutagenic effects of coffee may be particularly relevant to mutagenesis by heterocyclic amines, which are formed during the cooking of meat (48) and possibly related to colon carcinogenesis (49). Coffee contains at least two possible antagonists of the mutagenic effects of heterocyclic amines, an insoluble hemicellulose fiber, which can effectively adsorb mutagenic agents, and a high-molecular-weight polyphenol, which is able to destroy mutagenic agents in the alimentary tract when the polyphenol is converted to quinone derivatives (50).

Another potential mechanism is based on the influence of coffee consumption on fecal levels of cholesterol, bile acids, and their metabolites, which promote colon carcinogenesis in some animal studies (51, 52). Coffee consumption has been linked to increased serum cholesterol levels in some studies, particularly in Scandinavia (53–57). In the Northern European countries, coffee is usually prepared by boiling ground coffee beans with water and decanting the fluid without filtration. It is now known that serum cholesterol is raised by cafestol and possibly also kahweol (58), both lipid components of coffee beans, and that the lipid component of coffee is removed by filtration (59). If the mechanism, currently unknown, leading to higher cholesterol levels involves a reduced excretion of bile acids or neutral sterols, and if these compounds are related to colorectal cancer, the lower risk of colorectal cancer should be considerably stronger in countries that use boiled coffee. While strong inverse associations were seen in Finland, Sweden, and Norway, countries which use boiled coffee, similarly strong reductions in risk were also observed in Italy, Belgium, France, and Japan.

Finally, both regular and decaffeinated coffee induce an increase in colonic motility limited to the rectosigmoid region within 4 minutes of ingestion and lasting for at least 30 minutes (3). Unfortunately, the published studies did not allow for the examination of cancer risk associated with coffee intake specifically in the rectosigmoid region. This influence of coffee on rectosigmoid responses appeared primarily in men and women who claimed that coffee induced a desire to defecate (53 percent of women and 19 percent of men). The speed of the response indicated that coffee may induce a "gastrocolonic response," possibly by acting on receptors in the stomach or small bowel and mediated by neural mechanisms or by gastrointestinal hormones. Although unproven, colonic motility could be related to colonic cancer risk by influencing the exposure of the epithelia to colonic contents.

In summary, numerous studies have found a lower risk of colorectal cancer associated with higher coffee consumption. The data from case-control studies are remarkably consistent, while those from cohort studies are limited and inconclusive. A constant methodological artifact is unlikely to account for the relative consistency of the results in these diverse settings, although additional prospective data from several ongoing cohort studies (60–63) based on extensive dietary questionnaires will be informative. Presently, the most likely explanations of the lower risk of colorectal cancer among substantial coffee consumers are that unidentified high-risk individuals avoid coffee consumption, or that the association is causal and possibly related to enhanced colonic motility induced by coffee or to antimutagenic components in coffee.

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REFERENCES

1. Rosenberg L. Coffee and tea consumption in relation to the risk of large bowel cancer: a review of epidemiologic studies. Cancer Lett 1990;52:163–71.
2. Nehlig A, Debry G. Potential genotoxic, mutagenic and antimutagenic effects of coffee: a review. Mutat Res 1994;317:145–62.
3. Brown SR, Cann PA, Read NW. Effect of coffee on distal colon function. Gut 1990;30:450–3.
4. Kato I, Tominaga S, Matsuura A, et al. A comparative case-control study of colorectal cancer and adenoma. Jpn J Cancer Res 1990;81:1101–8.
5. Slattery ML, West DW, Robison LM, et al. Tobacco, alcohol, coffee, and caffeine as risk factors for colon cancer in a low-risk population. Epidemiology 1990;1:141–5.
6. Centonze S, Boeing H, Leoci C, et al. Dietary habits and colorectal cancer in a low-risk area. Results from a population-based case-control study in southern Italy. Nutr Cancer 1994;21:233–46.
7. Macquart-Moulin G, Riboli E, Cornee J, et al. Case-control study on colorectal cancer and diet in Marseilles. Int J Cancer 1986;38:183–91.
8. Benito E, Obrador A, Stiggelbout A, et al. A population-based case-control study of colorectal cancer in Majorca. Int J Cancer 1990;45:69–76.
9. Bidoli E, Franceschi S, Talamini R, et al. Food consumption and cancer of the colon and rectum in north-eastern Italy. Int J Cancer 1992;50:223–9.
10. La Vecchia C, Ferraroni M, Negri E, et al. Coffee consumption and digestive tract cancers. Cancer Res 1989;49:1049–51.

11. Lee HP, Gourley L, Duffy SW, et al. Colorectal cancer and diet in an Asian population—a case-control study among Singapore Chinese. Int J Cancer 1989;43:1007–16.
12. Tuyns AJ, Kaaks R, Haelterman M. Colorectal cancer and consumption of foods: a case-control study in Belgium. Nutr Cancer 1988;11:189–204.
13. Bjelke E. Colon cancer and blood-cholesterol. (Letter). Lancet 1974;1:1116–17.
14. Rosenberg L, Werler MM, Palmer JR, et al. The risks of cancers of the colon and rectum in relation to coffee consumption. Am J Epidemiol 1989;130:895–903.
15. Baron JA, Gerhardsson de Verdier M, Ekbom A. Coffee, tea, tobacco, and cancer of the large bowel. Cancer Epidemiol Biomarkers Prev 1994;3:565–70.
16. Wu AH, Paganini-Hill A, Ross RK, et al. Alcohol, physical activity, and other risk factors for colorectal cancer: a prospective study. Br J Cancer 1987;55:687–94.
17. Phillips RL, Snowdon DA. Dietary relationships with fatal colorectal cancer among Seventh-day Adventists. J Natl Cancer Inst 1985;34:307–17.
18. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994;5:401–8.
19. Klatsky AL, Armstrong MA, Friedman GD, et al. The relations of alcoholic beverage use to colon and rectal cancer. Am J Epidemiol 1988;128:1007–15.
20. Jacobsen BK, Bjelke E, Kvåle G, et al. Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. J Natl Cancer Inst 1986;76:823–31.
21. Suadicani P, Hein HO, Gyntelberg F. Height, weight, and risk of colorectal cancer. An 18-year follow-up in a cohort of 5249 men. Scand J Gastroenterol 1993;28:285–8.
22. Kono S, Imanishi K, Shinchi K, et al. Relationship of diet to small and large adenomas of the sigmoid colon. Jpn J Cancer Res 1993;84:13–19.
23. Morson B. President's address. The polyp-cancer sequence in the large bowel. Proc Soc Med 1974;67:451–7.
24. D'Amicis A, Viani R. The consumption of coffee. In: Garattini S, ed. Caffeine, coffee, and health. New York: Raven, 1993:1–16.
25. Boyd NF, Martin LJ, Noffel M, et al. A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer 1993;68:627–36.
26. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1–30.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
28. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113:779–88.
29. Haenszel W, Berg JW, Segi M, et al. Large-bowel cancer in Hawaiian Japanese. J Natl Cancer Inst 1973;51:1765–79.
30. Abu-Zeid HA, Choi NW, Hsu PH. Factors associated with risk of cancer of the colon and rectum. (Abstract). Am J Epidemiol 1981;114:442.
31. Dales LG, Friedman GD, Ury HK, et al. A case-control study of relationships of diet and other traits to colorectal cancer in American blacks. Am J Epidemiol 1979;109:132–44.
32. Young TB, Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. Int J Cancer 1988; 42:167–75.
33. Graham S, Dayal H, Swanson M, et al. Diet in the epidemiology of cancer of the colon and rectum. J Natl Cancer Inst 1978;61:709–14.
34. Peters RK, Pike MC, Garabrandt D, et al. Diet and colon cancer in Los Angeles County, California. Cancer Causes Control 1992;3:457–73.
35. Miller AB, Howe GR, Jain M, et al. Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. Int J Cancer 1983;32:155–61.
36. Gerhardsson M, Floderus B, Norell SE. Physical activity and colon cancer risk. Int Epidemiol 1988;17:743–6.
37. Nomura A, Heilbrun LK, Stemmermann GN. Prospective study of coffee consumption and the risk of cancer. J Natl Cancer Inst 1986;76:587–90.
38. Grobbee DE, Rimm EB, Giovannucci E, et al. Coffee, caffeine, and cardiovascular disease in men. N Engl J Med 1990;323:1026–32.
39. Herzog P, Holtermuller K-H, Preiss J, et al. Fecal blood loss in patients with colonic polyps: a comparison of measurements with 51chromium-labeled erythrocytes and with the Haemoccult test. Gastroenterology 1982;83:957–62.
40. Macrae FA, St John DJ. Relationship between patterns of bleeding and Hemeoccult sensitivity in patients with colorectal cancers or adenomas. Gastroenterology 1982;82:891–8.
41. Vineis P. Hypothesis: coffee consumption, *N*-acetyltransferase phenotype, and cancer. (Letter). J Natl Cancer Inst 1993;85:1004–5.
42. Ilett KF, David BM, Detchon P, et al. Acetylation phenotype in colorectal carcinoma. Cancer Res 1987;47:1466–9.
43. Lang NP, Chu DZL, Hunter CF, et al. Role of aromatic amine acetyltransferase in human colorectal cancer. Arch Surg 1986; 121:1259–61.
44. Probst-Hensch NM, Haile RW, Ingles SA, et al. Acetylation polymorphism and prevalence of colorectal adenomas. Cancer Res 1995;55:2017–20.
45. Ladero JM, Gonzalez JF, Benitez J, et al. Acetylator polymorphism in human colorectal carcinoma. Cancer Res 1991;51: 2098–2100.
46. Shibuta K, Nakashima T, Abe M, et al. Molecular genotyping for *N*-acetylation polymorphism in Japanese patients with colorectal cancer. Cancer 1994;74:3108–12.
47. Schreiber GB, Maffeo CE, Robins M, et al. Measurement of coffee and caffeine intake implications for epidemiologic research. Prev Med 1988;17:280–94.
48. Sugimura T, Sato S. Mutagens-carcinogens in foods. Cancer Res 1983;43:2415s-21s.
49. Turesky RJ, Lang N, Butler MA, et al. Metabolic activation of carcinogenic heterocyclic aromatic amines by human liver and colon. Carcinogenesis 1991;12:1417–21.
50. Kato TS, Takahashi S, Kikugawa K. Loss of heterocyclic amine mutagens by insoluble hemicellulose fiber and high-molecular-weight soluble polyphenolics of coffee. Mutat Res 1991;246:169–78.
51. Koga S, Kaibara N, Takeda R. Effect of bile acids on 1,2-dimethylhydrazine-induced colon cancer in rats. Cancer 1982; 50:543–7.
52. Narisawa T, Magadia NE, Weisburger JH, et al. Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in rats. J Natl Cancer Inst 1974;53:1093–7.
53. Thelle DS, Arnesen E, Forde OH. The Tromso Heart Study. Does coffee raise serum cholesterol? N Engl J Med 1983;308: 1454–7.
54. Thelle DS, Heyden S, Fodor JG. Coffee and cholesterol in epidemiological and experimental studies. Atherosclerosis 1987;67:97–103.
55. Bonaa K, Arnesen E, Thelle DS, et al. Coffee and cholesterol: is it all in the brewing? The Tromso Study. BMJ 1988;297: 1103–4.
56. Stensvold I, Tverdal A, Foss OP. The effect of coffee on blood lipids and blood pressure. Results from a Norwegian cross-sectional study, men and women, 40–42 years. J Clin Epidemiol 1989;42:877–84.
57. Pietinen P, Aro A, Tuomilehto J, et al. Consumption of boiled coffee is correlated with serum cholesterol in Finland. Int J Epidemiol 1990;19:586–90.
58. Weusten-Van der Wouw MPME, Katan MB, Viani R, et al. Identity of the cholesterol-raising factor from boiled coffee and its effects on liver function enzymes. J Lipid Res 1994; 35:721–33.
59. van Dusseldorp M, Katan MB, van Vliet T, et al. Cholesterol-raising factor from boiled coffee does not pass a paper filter. Arterioscler Thromb 1991;11:586–93.

60. Willett WC, Stampfer MJ, Colditz GA, et al. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990;323:1664–72.
61. Goldbohm RA, van den Brandt PA, van't Veer P, et al. A prospective cohort study on the relation between meat consumption and the risk of colon cancer. Cancer Res 1994;54: 718–23.
62. Bostick RM, Potter JD, Kushi LH, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 1994; 5:38–52.
63. Giovannucci E, Rimm EB, Stampfer MJ, et al. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54:2390–7.