

Coffee Intake Is Associated With Lower Risk of Symptomatic Gallstone Disease in Women

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Background & Aims: Metabolic studies have shown that coffee affects several hepatobiliary processes that are involved in cholesterol lithogenesis. We previously showed that coffee drinking was associated with a lower risk of symptomatic gallstone disease in men. **Methods:** We prospectively examined the association between coffee drinking and cholecystectomy, a surrogate of symptomatic gallstone disease, in a cohort of 80,898 women age 34–59 years in 1980 who had no history of gallstone disease. Coffee consumption and cholecystectomy were reported by participants on biennial mailed questionnaires. **Results:** During 20 years of follow-up to the year 2000, 7,811 women reported a cholecystectomy. Compared with women who consistently reported consuming no caffeinated coffee, the multivariate relative risks (adjusting for risk factors for gallstone disease) of cholecystectomy comparing increasing categories of consistent intake of caffeinated coffee (0, 1, 2–3, and ≥ 4 cups/day) were 1.0, 0.91, 0.78, and 0.72 (95% confidence interval comparing extreme categories, 0.62–0.84; P value of test for trend < 0.0001). Caffeine intake from beverages and dietary sources was also inversely associated with risk of cholecystectomy. The multivariate relative risks comparing increasing categories of caffeine intake (≤ 25 , 26–100, 101–200, 201–400, 401–800, and > 800 mg/day) were 1.0, 1.03, 1.01, 0.94, 0.85, and 0.85 (95% confidence interval comparing extreme categories, 0.74–0.96; P value of test for trend < 0.0001). In contrast, decaffeinated coffee was not associated with risk. **Conclusions:** These data suggest that consumption of caffeinated coffee may play a role in the prevention of symptomatic gallstone disease in women.

Gallstones are a major source of morbidity in the United States, where they affect more than 20 million individuals¹ and result in nearly 800,000 cholecystectomies each year, making gallbladder surgery one of the most common operations.² Coffee consumption is

widespread; almost 50% of Americans drink coffee, amounting to a per capita intake of 1.7 cups per day.³

Coffee affects several hepatobiliary processes that are involved in cholesterol gallstone formation. Coffee and individual coffee constituents stimulate cholecystokinin release,⁴ enhance gallbladder contractility,^{4,5} inhibit gallbladder fluid absorption,⁶ decrease cholesterol crystallization in bile,⁷ and perhaps increase intestinal motility.⁸ In addition, coffee diterpenes may down-regulate the hepatic low-density lipoprotein receptor⁹ and decrease 3-hydroxy-3-methylglutaryl CoA reductase activity.¹⁰ Thus, metabolic studies suggest that coffee consumption may influence gallstone formation.^{4–10}

Most,^{11–17} but not all, epidemiologic studies^{18–20} concerning the association between coffee consumption and risk of gallstone disease are compatible with decreased risk of gallstone disease in persons with high coffee intake. These findings may be due to an antilithogenic effect of 1 or more of the numerous ingredients present in coffee. Alternatively, the observed associations could be spurious if persons with latent gallstone symptoms tend to avoid coffee, thereby raising the gallbladder disease rate in the non-coffee-drinking group. We prospectively examined coffee, tea, decaffeinated coffee, caffeinated soft drinks, and caffeine from all sources, as well as coffee brewing methods, in relation to the risk for cholecystectomy in a cohort of women in the United States. We addressed whether noncausal mechanisms may have accounted for any observed association.

Materials and Methods

Study Population

In the Nurses' Health Study, 121,700 married female nurses age 30–55 years completed a mailed questionnaire on

their medical history and lifestyle characteristics in 1976. Every 2 years, follow-up questionnaires were sent to update information on potential risk factors and to identify newly diagnosed illnesses. In 1980, the questionnaire included an extensive assessment of diet. The present analysis is based on the 80,898 women who answered the 1980 diet questionnaire and did not have cancer, a cholecystectomy, or a gallstone diagnosis before 1980. This study was approved by the institutional review board on the use of human subjects in research of the Brigham and Women's Hospital in Boston.

Assessment of Coffee Intake and Diet

The consumption of regular coffee, tea, and chocolate candy was assessed in 1980 as part of a 61-item semiquantitative food-frequency questionnaire.²¹ For each item, participants were asked to report their average use over the past year with 9 prespecified responses ranging from never or almost never to ≥ 6 times per day. We updated the dietary assessment in 1984, 1986, 1990, and 1994. We calculated caffeine intake by multiplying the frequency of consumption of each beverage by the caffeine content of the specified portion size. Our assessment of coffee intake also included information on whether participants consumed mainly filtered, instant, or espresso-type coffee. In a validation study in a random sample of 173 Boston-area participants, the correlations between beverage intakes assessed by the diet questionnaire and by multiple-week dietary records were 0.78 for coffee, 0.93 for tea, and 0.84 for caffeinated soft drinks.²²

Identification of Cholecystectomy Cases

We inquired about occurrence and date of cholecystectomy on each biennial questionnaire starting in 1980. A validation study of the self-report was conducted in a random sample of 50 nurses who reported a cholecystectomy in 1982. Forty-three of 50 participants responded, and all 43 reiterated their earlier report. Surgery was confirmed in all 36 for whom medical records could be obtained.²³ We chose cholecystectomy as an endpoint mainly because women are more likely to accurately report the occurrence and timing of a surgical procedure than untreated gallstones.

Data Analysis

We calculated person-time of follow-up for each participant from the date of return of the 1980 questionnaire to the date of cholecystectomy, cancer, last questionnaire return, death, or the end of the study period in 2000, whichever came first. Women were divided into 4 categories according to their amount of coffee consumption: none, ≤ 1 cup/day, 2–3 cups/day, and ≥ 4 cups/day. We computed incidence rates of cholecystectomy by dividing the number of events by person-years of follow-up in each category. The relative risk was calculated as the incidence rate in a specific category of coffee intake divided by that in the lowest category of coffee intake, with adjustment for age in 5-year categories. Multivariate relative risks were computed using the Cox proportional hazards regression model.²⁴ We simultaneously adjusted for multiple

potential confounding variables to ensure that our results were not explained on the basis of other known determinants of gallstone disease, such as alcohol use.

To account for changes in coffee intake over time, we conducted our primary analyses using the most recent coffee intake. In alternative analyses, we analyzed the incidence of cholecystectomy in relation to coffee intake at baseline and to cumulative average updated coffee intake. We conducted various analyses to address the possibility that underlying symptoms related to cholecystectomy caused a reduction in coffee consumption and thus biased our results by creating spurious associations. In addition, we conducted an analysis to estimate the impact of measurement error in assessing coffee consumption²⁵ by using data from our validation study.²²

Results

At baseline in 1980, 77% of the participants reported drinking caffeinated coffee at least once per month. Compared with coffee abstainers, women who drank caffeinated coffee tended to smoke more, consume less dietary fiber, and exercise less, all of which would tend to increase gallstone risk. However, they drank more alcohol and were less likely to use hormone-replacement therapy, which would tend to decrease risk (Table 1). Women maintained fairly constant levels of coffee consumption throughout follow-up. The correlation coefficients for coffee intake ranged from 0.68 to 0.80 from 1 questionnaire to the next.

During 1,389,936 person-years of follow-up, we documented 7,811 cases of cholecystectomy. The risk of cholecystectomy decreased in a linear fashion with increasing consumption of caffeinated coffee (Table 2). Compared with women who consumed no caffeinated coffee, the multivariate relative risk for those who drank ≥ 4 cups of caffeinated coffee per day was 0.77 (95% confidence interval, 0.71–0.83). Because the category of coffee abstainers might have included women who did not drink coffee because of illness, we conducted an analysis excluding all coffee abstainers and using light coffee drinkers (up to 1 cup/day) as the reference group. The association remained materially unchanged (multivariate relative risk for women drinking ≥ 4 cups per day, 0.82; 95% confidence interval, 0.76–0.89).

To examine whether latent symptoms of gallstone disease may have caused a decrease in coffee consumption, thereby biasing our results, we repeated our analysis after excluding the first 4 years of follow-up and relating 1980 coffee intake to the incidence of cholecystectomy in 1984–2000. Compared with women who had no intake of caffeinated coffee, women who drank ≥ 4 cups of caffeinated coffee per day had a multivariate risk of 0.82 (95% confidence interval, 0.76–0.89). The findings were

Table 1. Baseline (1980) Characteristics of the 80,898 Study Women According to Category of Caffeinated Coffee Intake^a

Characteristic	Caffeinated coffee intake			
	None	≤1 cup/day	2–3 cups/day	≥4 cups/day
Participants (<i>n</i>)	18,609	15,755	26,412	20,122
Age (<i>yr</i>)	45.7	45.8	46.2	46.3
Body mass index (<i>kg/m</i> ²)	24.5	24.3	24.1	24.0
Any weight loss in prior 2 years (%)	30.5	29.2	28.9	29.6
Parity (number of births)	2.8	2.8	2.9	3.0
History of OC use (%)	49.7	50.9	49.7	48.8
HRT use (%) ^b	14.9	14.9	14.8	13.6
Current smokers (%)	19.4	19.6	27.4	45.7
Routine check-up in 1986–1988 (%)	81.0	80.7	80.0	78.4
History of diabetes (%)	2.8	2.2	1.7	1.8
Physical activity (hours per week)	3.1	3.0	3.0	2.9
Mean daily intakes				
Caffeine (<i>mg</i>)	115	188	410	781
Alcohol (<i>g</i>)	4.6	5.8	7.7	7.3
Total fat (<i>g</i>) ^c	69	69	70	71
Polyunsaturated fat (<i>g</i>) ^c	9	9	9	9
Carbohydrates (<i>g</i>) ^c	160	158	154	151
Dietary fiber (<i>g</i>) ^c	14.3	13.9	13.5	13.2
Magnesium (<i>mg</i>) ^{c,d}	262	269	297	336
Potassium (<i>mg</i>) ^{c,d}	2476	2534	2771	3159
Tea (<i>cups/week</i>)	9.5	7.0	5.4	4.0
Caffeinated soft drinks (<i>glasses/week</i>)	1.9	1.5	1.3	1.1

^aAll values (except age) are standardized according to the age distribution of the cohort.

^bHRT use among postmenopausal women only.

^cAdjusted for total energy intake.

^dWithout supplements.

virtually identical when we excluded the first 8 years of follow-up (multivariate relative risk comparing extreme categories, 0.82; 95% confidence interval, 0.77–0.89). Additional exclusion of women who did not have a routine medical check-up between 1986 and 1988 did not alter the relation materially (multivariate relative risk comparing extreme categories, 0.85; 95% confidence interval, 0.78–0.93).

To address the possibility that coffee drinkers may be less likely than coffee abstainers to undergo minor surgical procedures such as cholecystectomy because they are less health-conscious on average, we excluded all cases with cholecystectomy and limited the analysis to cases of symptomatic but unremoved gallstones that occurred during the 1980–1986 follow-up period. The multivariate relative risk of symptomatic gallstone disease for women consuming ≥4 cups of caffeinated coffee per day compared to women with no consumption of caffeinated coffee was 0.80 (95% confidence interval, 0.68–0.94).

We estimated the impact of measurement error in our assessment of coffee intake by using data from our validation study. An increase in caffeinated coffee consumption of 2 cups/day was associated with a relative risk of 0.93 (95% confidence interval, 0.91–0.96). After correction for measurement error, the relative risk was 0.79 (95% confidence interval, 0.70–0.88).

The inverse association was stronger among women with evidence of consistent coffee intake over time. Women who consistently reported drinking 2–3 cups of caffeinated coffee per day had a relative risk of 0.78 (95% confidence interval, 0.71–0.86), and those consistently drinking ≥4 cups of caffeinated coffee per day had a relative risk of 0.72 (95% confidence interval, 0.62–0.84) compared with women who consistently reported consuming no caffeinated coffee.

To address the effect of longer-term coffee use, we evaluated the association between baseline coffee intake and risk of cholecystectomy. The multivariate relative risk among women who drank ≥4 cups of caffeinated coffee compared with women who drank no caffeinated coffee was 0.83 (95% confidence interval, 0.77–0.88). Similar associations were observed when we used cumulative average updated exposure information (multivariate relative risk comparing users of ≥4 cups of caffeinated coffee with coffee abstainers, 0.79; 95% confidence interval, 0.73–0.86).

To determine whether greater coffee consumption conferred greater benefit, we compared women who drank ≥6 cups of caffeinated coffee per day with coffee abstainers. The multivariate relative risk was 0.82 (95% confidence interval, 0.73–0.93), suggesting no further

Table 2. Relative Risk of Cholecystectomy in Relation to Average Daily Intake of Different Beverages Types

Beverage type	Beverage intake				P value (trend)
	None	≤1 cup/day	2–3 cups/day	≥4 cups/day	
Caffeinated coffee					
Number of cases	2,418	2,200	2,214	979	
Person-years of follow-up	359,896	357,043	440,687	232,309	
Age-adjusted RR (95% CI)	1.0	0.90 (0.85–0.96)	0.75 (0.71–0.80)	1.19 (1.06–1.34)	<.0001
Multivariate RR (95% CI)	1.0	0.92 (0.87–0.98)	0.82 (0.78–0.87)	0.77 (0.71–0.83)	<.0001
Tea					
Number of cases	2,597	4,014	906	294	
Person-years of follow-up	482,468	695,876	162,112	49,480	
Age-adjusted RR (95% CI)	1.0	1.09 (1.04–1.14)	1.09 (1.01–1.17)	1.19 (1.06–1.34)	.007
Multivariate RR (95% CI)	1.0	1.07 (1.02–1.13)	1.06 (0.98–1.14)	1.13 (1.00–1.28)	.09
Decaffeinated coffee					
Number of cases	2,687	1,854	722	176	
Person-years of follow-up	428,116	289,910	115,630	29,685	
Age-adjusted RR (95% CI)	1.0	1.01 (0.95–1.07)	0.98 (0.91–1.07)	0.95 (0.82–1.11)	.43
Multivariate RR (95% CI)	1.0	1.01 (0.95–1.08)	0.96 (0.88–1.05)	0.93 (0.79–1.09)	.21
Caffeinated soft drinks (low-calorie types)					
Number of cases	3,194	1,968	225	43	
Person-years of follow-up	534,110	306,580	27,676	4,976	
Age-adjusted RR (95% CI)	1.0	1.10 (1.04–1.16)	1.45 (1.27–1.67)	1.59 (1.18–2.15)	<.0001
Multivariate RR (95% CI)	1.0	0.97 (0.92–1.04)	1.11 (0.96–1.28)	1.14 (0.83–1.55)	.09
Caffeinated soft drinks (regular types)					
Number of cases	3,860	1,492	67	11	
Person-years of follow-up	605,841	248,276	7,954	1,271	
Age-adjusted RR (95% CI)	1.0	1.00 (0.95–1.07)	1.51 (1.18–1.92)	1.60 (0.89–2.89)	.0004
Multivariate RR (95% CI)	1.0	1.09 (1.02–1.16)	1.42 (1.11–1.83)	1.41 (0.77–2.56)	.003

NOTE. All multivariate analyses were adjusted for age, body mass index at the beginning of each 2-year follow-up interval, weight change in the previous 2 years, parity, oral contraceptive use, hormone replacement therapy and menopausal status, physical activity, history of diabetes mellitus, pack-years of smoking, use of thiazide diuretics, nonsteroidal anti-inflammatory drugs, intake of energy-adjusted dietary fiber, energy-adjusted carbohydrates, alcohol, tea, caffeinated soft drinks, and caffeine-free soft drinks.

increase in risk reduction for more extreme levels of coffee intake.

To evaluate whether the relation between coffee use and the risk of cholecystectomy was modified by the duration of follow-up, we examined coffee use in association with cholecystectomy risk across strata of 4-year time intervals of follow-up. The effect of a given amount of caffeinated coffee intake did not change with duration of follow-up. We also investigated whether the apparent effect of coffee on the incidence of cholecystectomy varied across strata of women based on various risk factors for gallstone disease (Table 3). The associations between caffeinated coffee use and risk of cholecystectomy were similar across subgroups defined by age, body mass index, recent weight change, and postmenopausal hormone therapy.

We explored the relation between coffee brewing method and risk of cholecystectomy. For this analysis, we used 3430 cases of cholecystectomy occurring in 1990–2000 with no missing information on brewing method. We mutually adjusted brewing methods for each other by entering an indicator variable for each type of brewing method in the multivariate model. Using nondrinkers of

caffeinated coffee as the common reference group, the relative risk of cholecystectomy was 0.86 for women consuming any level of filtered coffee (95% confidence interval, 0.79–0.93), 0.82 for women consuming instant coffee (95% confidence interval, 0.74–0.92), and 0.83 for women consuming espresso (95% confidence interval, 0.72–0.96). The association between coffee use and risk of cholecystectomy was not significantly modified by brewing method (*P* value for test of interaction, 0.22).

We then examined the association between the total intake of caffeine from beverages and dietary sources and the risk for cholecystectomy. Caffeinated coffee contributed 79% of the total caffeine consumed by this population (followed by tea, with 13%). Higher intakes of caffeine were associated with a decreased risk of cholecystectomy. The relative risk for women in the highest category of caffeine intake (>800 mg/day) compared with women in the lowest category (≤25 mg per day) was 0.85 (95% confidence interval, 0.74–0.96). Because caffeine intake was highly correlated with coffee intake (*r* = 0.93), we did not model the 2 predictors simultaneously. When we modeled caffeine individually contributed by caffeinated coffee as a continuous variable,

Table 3. Relative Risk of Cholecystectomy in Relation to Intake of Caffeinated Coffee According to Selected Variables

Variable	Cases	Relative risk for intake of caffeinated coffee				P value (trend)
		None	≤1 cup/day	2–3 cups/day	≥4 cups/day	
Age						
≤49 years	1692	1.0	0.93	0.82	0.83	.004
50–59 years	3401	1.0	0.92	0.81	0.74	<.0001
≥60 years	2718	1.0	0.92	0.85	0.75	<.0001
Body mass index						
≤24	3124	1.0	0.89	0.81	0.76	<.0001
25–29	2578	1.0	0.90	0.79	0.76	<.0001
≥30	2109	1.0	0.97	0.90	0.78	.002
Recent weight change						
Loss of ≥5.0 lb	837	1.0	0.93	0.79	0.80	<.0001
Stable weight (change of ≤4.9 lb)	5637	1.0	0.92	0.83	0.78	<.0001
Gain of ≥5.0 lb	1337	1.0	0.96	0.83	0.67	.0001
PMH use						
Premenopausal	2691	1.0	0.94	0.79	0.78	<.0001
Never use	1763	1.0	0.99	0.89	0.78	.001
Current use	2537	1.0	0.89	0.84	0.79	.0004
Past use	820	1.0	0.89	0.79	0.65	.0005

NOTE. All multivariate analyses were adjusted for age, body mass index at the beginning of each 2-year follow-up interval, weight change in the previous 2 years, parity, oral contraceptive use, hormone replacement therapy and menopausal status, physical activity, history of diabetes mellitus, pack-years of smoking, use of thiazide diuretics, nonsteroidal anti-inflammatory drugs, intake of energy-adjusted dietary fiber, energy-adjusted carbohydrates, alcohol, tea, caffeinated soft drinks, and caffeine-free soft drinks.

the multivariate relative risk for an increment of 100 mg/day was 0.98 (95% confidence interval, 0.96–0.99). When we repeated this analysis with caffeine contributed by noncoffee sources, the multivariate relative risk for an increment of 100 mg/day was 1.05 (95% confidence interval, 1.01–1.10).

We observed no significant associations between the consumption of tea, decaffeinated coffee, or low-calorie caffeinated soft drinks and the risk of cholecystectomy. However, we found a positive association for increasing intakes of regular types of caffeinated soft drinks and cholecystectomy (*P* value of test for trend, 0.003) (Table 2).

Discussion

In this large prospective study of women, increased consumption of caffeinated coffee was associated with a considerably reduced risk of cholecystectomy. A consistent intake of ≥4 cups of coffee per day was associated with a >25% risk reduction. In our cohort, short-term coffee use may be of the most etiologic importance, because the strongest risk reduction was observed with most recent intake. The apparent effect of coffee was not modified by established risk factors for gallstone disease, and all brewing methods showed a decreased risk. Consumption of decaffeinated coffee or tea was not associated with risk, possibly due to the lower amount of caffeine in these beverages.²⁶ In addition,

our assessment of tea consumption did not allow us to distinguish between caffeinated and decaffeinated tea. We have no explanation for the observed positive association with caffeinated soft drinks, since we addressed the possibility of confounding by body mass index, recent weight loss, and carbohydrate intake. It is possible (though speculative) that women consuming caffeinated soft drinks may have undergone increased medical surveillance, resulting in an increased diagnosis of gallstones with subsequent cholecystectomy.

Of the few studies that have examined the relationship between coffee consumption and gallstone disease, most,^{11–17} but not all,^{18–20} are compatible with a decreased risk of gallstone disease in persons with high coffee intake. Statistically significant findings are limited to 2 prospective studies^{11,12} and 1 cross-sectional study.¹³ The relative risk estimates of cholecystectomy in the present study are consistent with these reports. One study in both genders reported an odds ratio of 0.62 for any vs. no coffee drinking,¹¹ 1 study in men observed a relative risk of 0.67 comparing ≥4 cups of coffee per day with abstention from coffee,¹² and 1 study in women found a decreased trend of prevalent gallbladder disease with increasing coffee consumption (*P* value of test for trend, 0.027).¹³

The main limitation of our study is that we investigated only gallstone disease resulting in cholecystectomy. No systematic screening procedures for the pres-

ence of asymptomatic gallstones were performed in the study population. Although we were not able to estimate the incidence of gallstone formation, we could estimate the incidence of newly symptomatic gallstone disease; thus our results may not be generalizable to the entire population with gallstone disease. Nonetheless, our analysis does focus on the clinically relevant fraction of gallstone disease.

Although coffee intolerance is not related to the presence of gallstones,²⁷ patients with symptomatic gallstone disease are sometimes advised to avoid coffee.²⁸ In addition, coffee appears to cause heartburn in certain individuals by diminishing lower esophageal sphincter pressure,²⁹ a disorder that may share a common pathogenesis with gallstone disease.³⁰

We were concerned about the possibility that the observed relation between coffee intake and cholecystectomy was caused by coffee avoidance among women with early symptoms related to gallstone disease, or that the inverse association was due to the existence of upper gastrointestinal symptoms related to both coffee use and gallstones. However, these biases are unlikely to have influenced our results substantially, because the inverse associations persisted after we excluded the first 4 and first 8 years of follow-up, when we used light coffee drinkers as the reference group, or when we excluded women without regular checkups, thus identifying women who may have consulted their physician more frequently because of reflux disease.

Coffee sensitivity is common in individuals with functional dyspepsia,³¹ a condition that may be due in part to heightened visceral nociception.³² In addition, consumers of large amounts of coffee show less health-seeking behavior than coffee abstainers³³ and thus may be less likely to undergo surgical procedures. The inverse association between coffee use and cholecystectomy would be spurious if cholecystectomies had been performed in patients who had asymptomatic gallstones coinciding with dyspeptic symptoms related to coffee sensitivity, or in patients with greater health-seeking behavior. However, the number of such unwarranted cases of cholecystectomy in our cohort would have had to be large to account for the observed results. Moreover, we observed similar results when we excluded cases with cholecystectomy and limited the analysis to cases of symptomatic but unremoved gallstones.

Measurement error in our assessment of coffee intake was a potential concern. However, we specifically corrected our estimates in a subanalysis. In addition, reporting of coffee consumption and other dietary factors has been extensively validated in subsamples of

the Nurses' Health Study cohort.²² Moreover, our prospective study design precluded bias attributable to differential recall of coffee consumption by women with and without cholecystectomy. Our findings are not likely caused by underascertainment of cholecystectomy cases, because this circumstance would not bias the observed relative risks.³⁴

The inverse association between coffee use and cholecystectomy is supported by laboratory studies showing that coffee or individual coffee constituents enhance gallbladder motility,^{4,5} improve gallbladder mucosal function,^{6,7} and may increase intestinal motility,⁸ factors related to reduced cholesterol lithogenesis.

A protective influence of coffee on gallstone formation could be due specifically to the effect of caffeine. Caffeine and other methylxanthines may prevent bile cholesterol supersaturation by stimulating ileal bile acid absorption,³⁵ increasing hepatic bile acid uptake,³⁶ decreasing serum estrogen levels,³⁷ increasing sex hormone-binding globulin concentrations,³⁸ and increasing thermogenesis and reducing body fat stores.³⁹ However, the inconsistent associations with caffeine from coffee and noncoffee sources argue against caffeine being the responsible ingredient.

Alternatively, it is possible that other ingredients in coffee contribute to the inverse relation. For example, coffee may act through the effects of magnesium, potassium, or niacin, which are coffee constituents^{40,41} and were inversely associated with cholecystectomy in our data. Coffee also contains an insoluble hemicellulose fiber⁴² that may decrease the colonic absorption of deoxycholic acid. In addition, coffee contains antioxidative substances, such as tocopherols⁴³ and caffeic acid,⁴⁴ capable of inhibiting reactive oxygen metabolites,⁴⁵ which appear to precede cholesterol crystallization.⁴⁶ These and other coffee components may be lost during industrial processing of decaffeinated coffee.⁴⁷ Coffee may also exert a protective influence on gallstone development through the effect of diterpenes, which are removed by filtering⁴⁸ and may modulate hepatic cholesterol metabolism, possibly by down-regulating the activity of sterol regulatory element-binding proteins.⁴⁹

In summary, these data suggest that moderate intake of caffeinated coffee may play a role in the prevention of symptomatic gallstone disease. This conclusion is supported by the evidence of a dose-response relationship, the existence of several plausible metabolic pathways, and the consistency with results from experimental studies.

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Received May 31, 2002. Accepted August 22, 2002.

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Supported by research grants (CA 87969, DK 46200) from the National Institutes of Health and by a National Cancer Institute Cancer Epidemiology Training Grant (5T32 CA09001-26, to M. L.).