Alcohol consumption in relation to risk of cholecystectomy in women[1–3]

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ABSTRACT

Background: Alcohol consumption has been linked to a lower risk of gallstone disease. However, the magnitude of the association is uncertain, and little is known about the relation of alcohol consumption patterns and individual types of alcoholic beverages to gallstone disease risk.

Objective: We prospectively examined the association between alcohol intake and cholecystectomy, a surrogate for symptomatic gallstone disease, in a large cohort of women.

Design: Women from the Nurses' Health Study who had no history of gallstone disease in 1980 (n = 80 898) were followed for 20 y. Alcohol consumption, which was measured every 2–4 y by food-frequency questionnaires, was used to predict subsequent cholecystectomy through multivariate analysis.

Results: We ascertained 7831 cases of cholecystectomy. Relative to subjects who had no alcohol intake, subjects who had alcohol intakes of 0.1–4.9, 5.0–14.9, 15.0–29.9, 30.0–49.9, and ≥ 50.0 g/d had multivariate relative risks of cholecystectomy of 0.95, 0.86, 0.80, 0.67, and 0.62 (95% CI: 0.49, 0.79), respectively. Relative to subjects who never consumed alcohol, subjects who consumed alcohol 1–2, 3–4, 5–6, and 7 d/wk had multivariate relative risks of cholecystectomy of 0.94, 0.88, 0.87, and 0.73 (0.63, 0.84), respectively. All alcoholic beverage types were inversely associated with cholecystectomy risk, independent of consumption patterns (for quantity of alcohol consumed, P = 0.04, 0.001, and 0.003 for wine, beer, and liquor, respectively; for frequency of alcohol consumption, P = 0.01, 0.07, and < 0.0001 for wine, beer, and liquor, respectively).

Conclusions: The intake of all alcoholic beverage types is inversely associated with the risk of cholecystectomy. Recommendations regarding the benefit of consuming moderate quantities of alcohol should be weighed against the potential health hazards. *Am J Clin Nutr* 2003;78:339–47.

KEY WORDS Alcohol, cholelithiasis, cholecystectomy, cohort, women

INTRODUCTION

Gallstones are a major source of morbidity in the United States, where they affect > 20 million persons (1) and result in nearly 800 000 cholecystectomies each year, making gallbladder surgery one of the most common operations (2). The results of most (3–25), but not all (26–34), epidemiologic investigations that addressed the relation between alcohol intake and gallstone disease suggest that alcohol confers protection against gallstone development. However, controversy exists regarding the magnitude of the inverse association between alcohol intake and cholelithiasis (35). Alternative explanations for the observed risk reduction include confounding by factors such as socioeconomic status or diet and bias from the inclusion of ill former drinkers in the reference group of nondrinkers.

Moreover, little is known about the relation between alcohol consumption patterns and the risk of gallstone disease. The pattern of "weekend drinking" has increased over time in the United States (36), and distinguishing between average alcohol intake and patterns of consumption may account for some of the inconsistencies found in epidemiologic studies of alcohol consumption and gallstone disease. In addition, information regarding the effect of specific types of alcoholic beverages on the risk of cholelithiasis is sparse (3–5). Of the 3 studies that addressed individual alcoholic beverage types, the results of one cohort study among women (3) and of one among both sexes (4) suggest that moderate consumption of wine may be more consistently associated with a reduced risk of gallstone disease than are moderate intakes of beer and liquor. In contrast, the results of one cohort study among men (5) indicate that all alcoholic beverage types are inversely associated with the risk of gallstone disease.

In 1989 we reported an inverse association between alcohol intake and the risk of symptomatic gallstone disease among women enrolled in the Nurses' Health Study (3). The first study report was based on a single assessment of alcohol with follow-up from 1980 to 1984 and on 612 incident cases of symptomatic gallstone disease. The present analyses extend that finding by evaluating in detail the effects of the total amount of alcohol consumed; the frequency of total alcohol consumption; alcohol consumption patterns; and alcohol consumption from beer, wine, and liquor on the basis of multiple assessments of alcohol intake from 1980 to 1998 and 7831 cases of cholecystectomy.

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[2] Supported by research grants CA 87969 and DK 46200 from the National Institutes of Health, research grant AA11181 from the National Institute on Alcohol Abuse and Alcoholism, and a Cancer Epidemiology Training Grant (5T32 CA09001-26, to MFL) from the National Cancer Institute.

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Received November 15, 2002.

Accepted for publication March 31, 2003.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study was initiated when 121 700 married female nurses aged 30–55 y completed a mailed questionnaire on their medical history and lifestyle characteristics in 1976. Every 2 y, 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 (29 625 women excluded) and who did not have a cholecystectomy or a gallstone diagnosis before 1980 (7926 women excluded) or a diagnosed cancer other than nonmelanoma skin cancer at baseline (3251 women excluded). The 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 alcohol intake

The consumption of wine, beer, and liquor was assessed in 1980 as part of a 61-item, semiquantitative food-frequency questionnaire (37). For each item, participants were asked to report their average intake over the past year with 9 prespecified responses ranging from never or almost never to ≥6 times/d. We updated alcohol assessment, with the addition of white wine and red wine intakes, in 1984, 1986, 1990, 1994, and 1998. Standard portion sizes were specified as one 4-oz (118 mL) glass for wine; one glass, bottle, or 12-oz (354 mL) can for beer; and one measure (45 mL) for liquor. The alcohol content was calculated as 11.3 g for a glass of wine; 12.8 g for a glass, bottle, or can of beer; and 14.0 g for a shot or drink of liquor. The total alcohol intake for each participant was computed as the sum of the contributions from wine, beer, and liquor.

To distinguish between a pattern of frequent, moderate drinking and a pattern of infrequent, heavy drinking, our assessment of alcohol intake also included information on the average number of days per week that any type of alcoholic beverage was consumed. Because the frequency of alcohol consumption was first reported in 1986, in the analyses involving frequency of alcohol intake, we began follow-up in 1986 and excluded women who had a cholecystectomy or a diagnosis of gallbladder disease before the 1986 questionnaire was returned. To examine the individual effects of wine, beer, and liquor, we identified a predominantly consumed alcoholic beverage for each subject, ie, the beverage type of which most portions of alcohol were consumed. Women who reported an equal consumption of individual alcoholic beverage types were considered separately.

The validity and reproducibility of the food-frequency questionnaire were assessed in a random sample of 173 participants who completed 2 questionnaires and four 1-wk diet records and provided a fasting blood sample (38). Alcohol intake over the previous year, as reported on the second questionnaire, correlated highly with intake assessed by the four 1-wk diet records completed over this period (Spearman $r = 0.90$). Serum HDL-cholesterol concentrations were significantly correlated with alcohol intakes as measured by the questionnaire ($r = 0.40$, $P < 0.0001$) and by the diet records ($r = 0.33$, $P < 0.001$).

Identification of cases of cholecystectomy

Starting in 1980, we inquired about the occurrence and the date of cholecystectomy on each biennial questionnaire. A validation study of the self-reports was conducted in a random sample of 50 nurses who reported a cholecystectomy in 1982. Forty-three of the 50 participants responded, and all of them reiterated their earlier report; surgery was confirmed in all of the 36 participants for whom medical records could be obtained (3). We chose cholecystectomy as our primary endpoint mainly because women are more likely to accurately report the occurrence and timing of a surgical procedure than to accurately report the occurrence and timing of untreated gallstones. Moreover, 80% of the women in our cohort who had a cholecystectomy between 1980 and 1986 reported a diagnosis of symptomatic gallstone disease during that time period. In an alternative analysis to address the association between alcohol intake and less severe forms of gallstone disease, we limited our analysis to women who had symptomatic but unremoved gallstones during the 1980–1982, 1982–1984, and 1984–1986 follow-up intervals but who did not have a cholecystectomy in the same 2-y time interval.

Data analysis

We calculated person-years 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. The women were divided into 6 categories according to the amount of alcohol consumed: 0, 0.1–4.9, 5.0–14.9, 15.0–29.9, 30.0–49.9, and ≥50.0 g/d. We computed incidence rates of cholecystectomy by dividing the number of events by person-years of follow-up in each category. The relative risk (RR) was calculated as the incidence rate among subjects in a specific category of alcohol intake divided by the incidence rate among alcohol abstainers, with adjustment for age in 5-y categories.

Multivariate RRs were computed by using the Cox proportional hazards regression model (39). The covariates that were selected were those that were previously observed to be associated with gallstone disease in this cohort or that have been consistently found to be associated with risk in the literature. Tests of linear trend across increasing categories of alcohol intake were conducted by treating the median value in each alcohol-intake category as a single continuous variable.

To account for changes in alcohol intake over time, we used the most recent alcohol intake in our primary analyses. In alternative analyses, we analyzed the incidence of cholecystectomy in relation to alcohol intake at baseline and in relation to cumulative average, updated alcohol intake. The cumulative average intake is the mean of the reported intakes from all preceding food-frequency questionnaires (40). We conducted various analyses to address the possibility that underlying symptoms related to cholecystectomy caused a reduction in alcohol consumption, thereby biasing our results by creating spurious associations. Tests for interaction were performed with the use of Wald tests. All RRs are presented with 95% CIs, and reported P values are based on two-sided tests. All statistical analyses were conducted by using SAS release 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

At baseline in 1980, 69% of the participants reported drinking alcohol ≥1 time/mo. Among the women who consumed alcohol,

TABLE 1
Baseline characteristics in 1980 according to category of alcohol intake in 80 898 US women who participated in the Nurses' Health Study[1]

	Alcohol intake (g/d)						
	0 (n = 25 422)	0.1–4.9 (n = 27 104)	5.0–14.9 (n = 18 412)	15.0–29.9 (n = 5756)	30.0–49.9 (n = 3527)	≥50.0 (n = 677)	P for trend
Current HRT (%)	6.1	6.0	6.5	7.1	7.1	7.0	0.0006
Current smoker (%)	22	27	32	34	52	61	<0.0001
History of diabetes (%)	3.4	1.6	1.0	1.0	1.3	1.6	<0.0001
Regular aspirin use (%)[2]	44	47	48	49	48	50	<0.0001
Regular thiazide diuretic use (%)	9	9	9	11	14	15	<0.0001
Regular exercise (%)	41	46	49	51	44	38	<0.0001
Age (y)	46.0 ± 7.3[3]	45.8 ± 7.3	46.2 ± 7.1	46.5 ± 6.8	46.7 ± 6.7	46.8 ± 6.7	<0.0001
Alcohol intake (g/d)							
Wine	0	1.1 ± 1.2	4.2 ± 3.9	10.1 ± 8.9	8.3 ± 11.6	15.3 ± 20.0	<0.0001
Beer	0	0.2 ± 0.5	1.6 ± 3.0	2.9 ± 4.2	8.7 ± 12.9	25.7 ± 29.3	<0.0001
Liquor	0	0.6 ± 0.7	3.8 ± 4.2	7.9 ± 5.5	20.2 ± 15.7	26.1 ± 26.9	<0.0001
Current BMI (kg/m^2)	25.0 ± 4.9	24.3 ± 4.3	23.4 ± 3.6	23.1 ± 3.4	23.3 ± 3.5	23.7 ± 3.9	<0.0001
Parity (n)	2.90 ± 1.6	2.93 ± 1.6	2.90 ± 1.6	2.89 ± 1.6	2.87 ± 1.7	2.94 ± 1.7	0.02
Intake							
Total energy (kcal/d)[4]	1572 ± 512	1529 ± 490	1486 ± 476	1485 ± 483	1448 ± 481	1544 ± 540	<0.0001
Polyunsaturated fat (g/d)[5]	9.6 ± 2.9	9.5 ± 2.7	9.3 ± 2.7	8.8 ± 2.6	8.1 ± 2.6	6.7 ± 2.3	<0.0001
Carbohydrates (g/d)[5]	165 ± 37	160 ± 35	148 ± 33	136 ± 33	124 ± 33	117 ± 32	<0.0001
Coffee (cups/d)[6]	2.0 ± 2.1	2.3 ± 2.1	2.5 ± 2.0	2.6 ± 1.9	2.7 ± 2.0	2.8 ± 2.2	<0.0001

[1] Age adjusted by direct standardization to the age distribution of the study population. HRT, hormone replacement therapy (postmenopausal women only).
[2] Defined as aspirin use in most weeks during the previous 2 y.
[3] $\bar{x}$ ± SD.
[4] Excluding energy from alcohol.
[5] Adjusted for total energy intake.
[6] 1 cup = 237 mL.

82% reported low intakes (0.1–14.9 g/d), 17% had moderate to high intakes (15.0–49.9 g/d), and 1% had high intakes (≥50.0 g/d). Compared with the alcohol abstainers, the women who drank alcohol were more likely to receive hormone replacement therapy and to smoke and were less likely to exercise and to consume polyunsaturated fat, all of which would tend to increase gallstone disease risk. However, the alcohol drinkers had a slightly lower body mass index and a considerably lower intake of carbohydrates and drank more coffee, all of which would tend to decrease risk (**Table 1**). The women maintained fairly constant alcohol intakes throughout follow-up. The correlation coefficients for alcohol intake from one questionnaire to the next ranged from 0.63 to 0.81.

During 1 393 256 person-years of follow-up, we documented 7831 cases of cholecystectomy. Established risk factors showed expected relations with gallstone disease, and these results were consistent with those of previous reports from this cohort (3). The risk of cholecystectomy decreased in a linear fashion with increasing consumption of alcohol (**Table 2**). The multivariate RR associated with a 15-g/d increment in alcohol consumption was 0.87 (95% CI: 0.83, 0.90). Because the nondrinker category may have included past heavy drinkers or women who did not drink because of illness, we conducted an additional analysis that excluded women who were current nondrinkers in 1980 and who also indicated having substantially decreased their drinking in the past 10 y (past heavy drinkers). The association remained unchanged from that for the total cohort (multivariate RR for a 15-g alcohol/d increment: 0.86; 95% CI: 0.82, 0.89). In a subsequent analysis excluding all abstainers, the multivariate RR for a 15-g/d increment in alcohol consumption was 0.88 (95% CI: 0.84, 0.92).

To further examine the possibility that latent symptoms of gallstone disease may have caused a decrease in alcohol consumption, thereby biasing our results, we excluded all cases of gallstone disease that occurred during the first 8-y follow-up period and related the 1980 alcohol intake to the incidence of cholecystectomy from 1988 to 2000. The multivariate RR for a 15-g alcohol/d increment at baseline was 0.91 (95% CI: 0.86, 0.96). Additional exclusion of women who did not have a routine medical checkup between 1986 and 1988 had no effect (multivariate RR for a 15-g alcohol/d increment: 0.92; 95% CI: 0.86, 0.98).

To evaluate the effect of alcohol on gallstone disease that did not require surgery, 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 (Table 2). The multivariate RR for a 15-g alcohol/d increment was 0.72 (95% CI: 0.66, 0.79).

We addressed the effect of alcohol intake in the more distant past by evaluating the association between baseline alcohol intake and the risk of cholecystectomy. The multivariate RR for a 15-g alcohol/d increment was 0.88 (95% CI: 0.85, 0.92). When we used cumulative updated intake information, the multivariate RR for a 15-g alcohol/d increment was 0.82 (95% CI: 0.78, 0.86). The inverse association was evident among the women who had a consistent alcohol intake over time. Considering only the cases of cholecystectomy that occurred after 1984, the multivariate RR for a 15-g alcohol/d increment among the women who reported drinking alcohol on the 1980 and 1984 questionnaires was 0.82 (95% CI: 0.76, 0.88).

The average number of days per week in which alcohol was consumed was also inversely related to the risk of cholecystectomy (**Table 3**). Compared with the abstainers, the women who

TABLE 2
Relative risks (RRs) of cholecystectomy (1980–2000) and newly symptomatic unremoved gallstones (1980–1986) according to category of alcohol intake in 80 898 US women who participated in the Nurses' Health Study

	No. of cases	No. of person-years	RR (95% CI)	
			Age-adjusted[1]	Multivariate[2]
Cholecystectomy				
0 g/d	3870	606 029	Reference	Reference
0.1–4.9 g/d	2174	382 882	0.92 (0.87, 0.97)	0.95 (0.89, 1.00)
5.0–14.9 g/d	1161	250 997	0.74 (0.69, 0.79)	0.86 (0.80, 0.93)
15.0–29.9 g/d	376	86 923	0.68 (0.61, 0.76)	0.80 (0.72, 0.89)
30.0–49.9 g/d	172	47 794	0.56 (0.48, 0.66)	0.67 (0.57, 0.78)
≥50.0 g/d	78	18 631	0.62 (0.50, 0.78)	0.62 (0.49, 0.79)
P for trend			<0.0001	<0.0001
Newly symptomatic unremoved gallstones[3]				
0 g/d	1031	145 925	Reference	Reference
0.1–4.9 g/d	714	135 889	0.77 (0.70, 0.85)	0.81 (0.73, 0.89)
5.0–14.9 g/d	365	92 535	0.57 (0.50, 0.64)	0.67 (0.59, 0.76)
15.0–29.9 g/d	98	30 470	0.46 (0.37, 0.56)	0.56 (0.45, 0.70)
≥30.0 g/d	70	22 205	0.43 (0.34, 0.55)	0.46 (0.36, 0.59)
P for trend			<0.0001	0.0002

[1] RR calculated as the Mantel-Haenszel summary rate ratio, with adjustment for age in 5-y categories.

[2] RR computed by using Cox proportional hazards regression, with adjustment for time period (1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), age (<49, 50–54, 55–59, 60–64, ≥65 y), BMI (in kg/m^2) at the beginning of each 2-y follow-up interval (<20.00, 20.00–22.49, 22.50–24.99, 25.00–27.49, 27.50–29.99, 30.00–32.49, 32.50–34.99, 35.00–37.49, 37.50–39.99, ≥40), weight change in the previous 2 y [≥10 lb (4.5 kg) of weight loss, 5.0–9.9 lb (2.25–4.46 kg) of weight loss, maintained weight ± 4.9 lb (2.2 kg), 5.0–9.9 lb (2.25–4.46 kg) of weight gain, ≥10 lb (4.5 kg) of weight gain], parity (0, 1, 2–3, ≥4 births), oral contraceptive use (ever or never), hormone replacement therapy (premenopausal, postmenopausal without hormone replacement therapy, postmenopausal with past hormone replacement therapy, and postmenopausal with current hormone replacement therapy), physical activity (quintiles), history of diabetes mellitus (yes or no), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, ≥65), use of thiazide diuretics (yes or no), energy-adjusted fiber intake (quintiles), energy-adjusted carbohydrate intake (quintiles), energy-adjusted polyunsaturated fat intake (quintiles), and coffee intake (0, 1, 2–3, ≥4 cups/d; 1 cup = 237 mL).

[3] The analysis of women with newly symptomatic unremoved gallstones was based on the 1980–1986 follow-up period, so the number of person-years is smaller. The top 2 categories of alcohol intake were combined because of the small number of cases.

reported drinking 7 d/wk had a multivariate RR of 0.73 (95% CI: 0.63, 0.84). When frequency of alcohol intake was modeled simultaneously with the residual of frequency-adjusted grams of alcohol intake, the multivariate RR for the women who drank 7 d/wk, relative to that of the abstainers, was 0.71 (95% CI: 0.61, 0.82). The residual analysis was performed to avoid colinearity between frequency of alcohol intake and grams of alcohol intake (Spearman r = 0.81). We regressed grams of daily alcohol intake on

TABLE 3
Relative risk (RR) of cholecystectomy according to frequency of alcohol intake in 58 374 US women who participated in the Nurses' Health Study (1986–2000)[1]

			RR (95% CI)	
Frequency of alcohol intake	No. of cases	No. of person-years	Age-adjusted[2]	Multivariate[3]
0 d/wk	2702	365 431	Reference	Reference
1–2 d/wk	841	137 062	0.84 (0.78, 0.91)	0.94 (0.86, 1.01)
3–4 d/wk	296	56 228	0.72 (0.64, 0.81)	0.88 (0.77, 0.99)
5–6 d/wk	268	51 240	0.70 (0.62, 0.80)	0.87 (0.76, 0.99)
7 d/wk	229	52 460	0.58 (0.50, 0.66)	0.73 (0.63, 0.84)
P for trend			<0.0001	<0.0001

[1] The analysis was based on the 1986–2000 follow-up period, so the number of women studied is smaller than that studied during the entire study (ie, from 1980 to 2000).

[2] RR calculated as the Mantel-Haenszel summary rate ratio, with adjustment for age in 5-y categories.

[3] RR computed by using Cox proportional hazards regression, with adjustment for time period (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), age (<49, 50–54, 55–59, 60–64, ≥65 y), BMI (in kg/m^2) at the beginning of each 2-y follow-up interval (<20.00, 20.00–22.49, 22.50–24.99, 25.00–27.49, 27.50–29.99, 30.00–32.49, 32.50–34.99, 35.00–37.49, 37.50–39.99, ≥40), weight change in the previous 2 y [≥10 lb (4.5 kg) of weight loss, 5.0–9.9 lb (2.25–4.46 kg) of weight loss, maintained weight ± 4.9 lb (2.2 kg), 5.0–9.9 lb (2.25–4.46 kg) of weight gain, ≥10 lb (4.5 kg) of weight gain], parity (0, 1, 2–3, ≥4 births), oral contraceptive use (ever or never), hormone replacement therapy (premenopausal, postmenopausal without hormone replacement therapy, postmenopausal with past hormone replacement therapy, and postmenopausal with current hormone replacement therapy), physical activity (quintiles), history of diabetes mellitus (yes or no), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, ≥65), use of thiazide diuretics (yes or no), energy-adjusted fiber intake (quintiles), energy-adjusted carbohydrate intake (quintiles), energy-adjusted polyunsaturated fat intake (quintiles), and coffee intake (0, 1, 2–3, ≥4 cups/d; 1 cup = 237 mL).

TABLE 4
Relative risk (RR) of cholecystectomy according to alcohol consumption patterns in 58 374 US women who participated in the Nurses' Health Study (1986–2000)[1]

Alcohol consumption pattern	Intake per drinking day[2]	No. of cases	No. of person-years	RR (95% CI)	
				Age-adjusted[3]	Multivariate[4]
	g				
1–2 d/wk					
0 g/d	0	2702	365 431	Reference	Reference
<15.0 g/d	19.2	791	130 113	0.84 (0.78, 0.91)	0.92 (0.85, 1.00)
≥15.0 g/d	140.7	50	6949	0.94 (0.71, 1.25)	0.98 (0.74, 1.30)
P for trend				0.0004	0.09
3–4 d/wk					
0 g/d	0	2702	365 431	Reference	Reference
<15.0 g/d	15.1	239	45 825	0.71 (0.62, 0.81)	0.86 (0.75, 0.99)
≥15.0 g/d	59.7	57	10 403	0.74 (0.57, 0.96)	0.87 (0.67, 1.14)
P for trend				0.0001	0.10
5–6 d/wk					
0 g/d	0	2702	365 431	Reference	Reference
<15.0 g/d	12.1	175	30 128	0.78 (0.67, 0.91)	0.95 (0.81, 1.11)
≥15.0 g/d	38.9	93	21 112	0.59 (0.48, 0.73)	0.71 (0.58, 0.88)
P for trend				<0.0001	0.09
7 d/wk					
0 g/d	0	2702	365 431	Reference	Reference
<15.0 g/d	10.3	102	17 873	0.75 (0.61, 0.91)	0.88 (0.72, 1.08)
≥15.0 g/d	37.9	127	34 587	0.49 (0.41, 0.58)	0.61 (0.51, 0.74)
P for trend				<0.0001	<0.0001

[1] The analysis was based on the 1986–2000 follow-up period, so the number of women studied is smaller than that studied during the entire study (ie, from 1980 to 2000). $P = 0.07$ for the interaction between frequency of alcohol intake (d/wk) and quantity of alcohol consumed.

[2] $\bar{x}$.

[3] RR calculated as the Mantel-Haenszel summary rate ratio, with adjustment for age in 5-y categories.

[4] RR computed by using Cox proportional hazards regression, with adjustment for time period (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), age (<49, 50–54, 55–59, 60–64, ≥65 y), BMI (in kg/m^2) at the beginning of each 2-y follow-up interval (<20.00, 20.00–22.49, 22.50–24.99, 25.00–27.49, 27.50–29.99, 30.00–32.49, 32.50–34.99, 35.00–37.49, 37.50–39.99, ≥40), weight change in the previous 2 y [≥10 lb (4.5 kg) of weight loss, 5.0–9.9 lb (2.25–4.46 kg) of weight loss, maintained weight ± 4.9 lb (2.2 kg), 5.0–9.9 lb (2.25–4.46 kg) of weight gain, ≥10 lb (4.5 kg) of weight gain], parity (0, 1, 2–3, ≥4 births), oral contraceptive use (ever or never), hormone replacement therapy (premenopausal, postmenopausal without hormone replacement therapy, postmenopausal with past hormone replacement therapy, and postmenopausal with current hormone replacement therapy), physical activity (quintiles), history of diabetes mellitus (yes or no), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, ≥65), use of thiazide diuretics (yes or no), energy-adjusted fiber intake (quintiles), energy-adjusted carbohydrate intake (quintiles), energy-adjusted polyunsaturated fat intake (quintiles), and coffee intake (0, 1, 2–3, ≥4 cups/d; 1 cup = 237 mL).

frequency of alcohol intake by using linear regression, thereby creating for each woman a variable representing grams of alcohol intake uncorrelated with frequency of alcohol intake.

We investigated the effect of drinking patterns on the risk of cholecystectomy by combining the reports for quantity of alcohol consumed with those for frequency of alcohol intake (**Table 4**). Relative to abstention from alcohol, a high alcohol intake (ie, ≥15.0 g/d) tended to be more strongly related to a decreased risk of cholecystectomy among the women who frequently consumed alcohol than among those who consumed alcohol infrequently (P for interaction = 0.07).

We also examined drinking patterns for specific beverages. The 3-way interaction term based on the product of beverage type, grams of alcohol intake, and frequency of alcohol intake was not significant ($P = 0.21$). The 2-way interaction term based on the product of beverage type and quantity of alcohol consumed was not significant ($P = 0.79$) (**Table 5**), and neither was the 2-way interaction term based on the product of beverage type and frequency of alcohol intake ($P = 0.38$) (**Table 6**), indicating that the relation of a given amount of alcohol consumed or of a given frequency of alcohol intake to the risk of cholecystectomy did not differ by beverage type. Among the women who predominantly drank wine, beer, or liquor, the P values for the main effects of quantity of alcohol consumed were 0.04, 0.001, and 0.003, respectively. The P values for the main effects of frequency of alcohol intake among the women who predominantly drank wine, beer, or liquor were 0.01, 0.07, and <0.0001, respectively.

DISCUSSION

In this large prospective cohort study among women, we found that an increase in the amount of alcohol consumed or in the frequency of alcohol consumption was associated with a monotonic decrease in the risk of cholecystectomy. All types of alcoholic beverage were inversely associated with the risk of cholecystectomy, even after patterns of consumption were accounted for. These associations persisted after control for established or suspected independent risk factors for gallstone disease, such as body mass index, weight change, parity, and other variables. The apparent protective effect of alcohol was particularly striking when we considered symptomatic but unremoved gallstones as an endpoint. This suggests that alcohol consumption is inversely related to the early stages of gallstone formation but is less strongly associated with prevention of cholecystitis once gallstones have developed.

TABLE 5
Relative risk (RR) of cholecystectomy according to average daily alcohol intake among 58 374 US women who participated in the Nurses' Health Study (1986–2000) and for whom wine, beer, or liquor was the predominant type of alcoholic beverage consumed[1]

Predominant beverage consumed[2]	No. of cases[3]	No. of person-years	RR (95% CI)	
			Age-adjusted[4]	Multivariate[5]
Wine				
0 g/d	2702	365 431	Reference	Reference
<15.0 g/d	640	117 830	0.75 (0.69, 0.82)	0.89 (0.82, 0.98)
≥15.0 g/d	113	25 461	0.60 (0.50, 0.73)	0.79 (0.65, 0.96)
Beer				
0 g/d	2702	365 431	Reference	Reference
<15.0 g/d	139	20 594	0.93 (0.79, 1.11)	1.03 (0.87, 1.23)
≥15.0 g/d	50	13 055	0.51 (0.38, 0.67)	0.57 (0.43, 0.76)
Liquor				
0 g/d	2702	365 431	Reference	Reference
<15.0 g/d	262	44 472	0.79 (0.79, 0.90)	0.90 (0.79, 1.03)
≥15.0 g/d	119	26 671	0.59 (0.49, 0.71)	0.72 (0.59, 0.87)

[1] The analysis was based on the 1986–2000 follow-up period, so the number of women studied is smaller than that studied during the entire study (ie, from 1980 to 2000). Indicator variables for wine, beer, and liquor consumption were simultaneously entered in the model. The interaction between beverage type and quantity of alcohol consumed was not significant.

[2] Defined as the beverage type of which most portions of alcohol were consumed.

[3] Three hundred eleven cases who reported equal consumption of individual alcoholic beverage types were included in the model but are not shown.

[4] RR calculated as the Mantel-Haenszel summary rate ratio, with adjustment for age in 5-y categories.

[5] RR computed by using Cox proportional hazards regression, with adjustment for time period (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), age (<49, 50–54, 55–59, 60–64, ≥65 y), BMI (in kg/m^2) at the beginning of each 2-y follow-up interval (<20.00, 20.00–22.49, 22.50–24.99, 25.00–27.49, 27.50–29.99, 30.00–32.49, 32.50–34.99, 35.00–37.49, 37.50–39.99, ≥40), weight change in the previous 2 y [≥10 lb (4.5 kg) of weight loss, 5.0–9.9 lb (2.25–4.46 kg) of weight loss, maintained weight ± 4.9 lb (2.2 kg), 5.0–9.9 lb (2.25–4.46 kg) of weight gain, ≥10 lb (4.5 kg) of weight gain], parity (0, 1, 2–3, ≥4 births), oral contraceptive use (ever or never), hormone replacement therapy (premenopausal, postmenopausal without hormone replacement therapy, postmenopausal with past hormone replacement therapy, and postmenopausal with current hormone replacement therapy), physical activity (quintiles), history of diabetes mellitus (yes or no), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, ≥65), use of thiazide diuretics (yes or no), energy-adjusted fiber intake (quintiles), energy-adjusted carbohydrate intake (quintiles), energy-adjusted polyunsaturated fat intake (quintiles), and coffee intake (0, 1, 2–3, ≥4 cups/d; 1 cup = 237 mL).

We have no information on whether alcohol protects against clinically asymptomatic gallstones, because the outcomes in our data set were limited to women with cholecystectomy or confirmed gallstones with accompanying symptoms.

Our findings regarding total alcohol intake confirm those of most other reports on this topic, which indicate that alcohol consumption is inversely related to the risk of gallstone disease (3–25). A French case-control study (25) found that, relative to alcohol abstainers, subjects who had an alcohol intake of 30 g/d had an odds ratio for ultrasound-detected gallstones of 0.28 (95% CI: 0.08, 0.95). In the Framingham study (7), women who consumed ≥30 g alcohol/d had an RR of gallbladder disease of 0.63 (95% CI: 0.39, 1.01). Similarly, a case-control study from Greece (11) observed that, relative to alcohol abstainers, subjects who consumed alcohol 3–4 d/wk had an odds ratio of gallstone disease of 0.7 (95% CI: 0.5, 0.9).

Our results regarding the relation of individual types of alcoholic beverage to the risk of cholecystectomy extend the results of our first report from the Nurses' Health Study with 612 cases of symptomatic gallstone disease (3). In that report, we found RRs of 0.7 (95% CI: 0.5, 1.0), 0.8 (95% CI: 0.5, 1.1), and 1.0 (95% CI: 0.8, 1.2) for intakes of ≥5 g alcohol/d from wine, beer, and liquor, respectively. In our previous study among men (5), the RRs of symptomatic gallstone disease for an alcohol intake ≥15 g/d were 0.59 (95% CI: 0.43, 0.81), 0.68 (95% CI: 0.49, 0.92), and 0.75 (95% CI: 0.61, 0.94) for men who predominantly drank wine, beer, or liquor, respectively. An Italian cohort study (4) found an inverse association for wine intake at 30 g/d (odds ratio: 0.71; 95% CI: 0.54, 0.92) but not for beer or liquor at the same intake, which may have been due to the study's comparatively small sample size or to a low variability in beer and liquor intake in that population.

Some investigators (35) have argued that the inverse association between alcohol intake and gallstone disease observed in most studies is an artifact caused by a reduction in alcohol intake among persons with early symptoms related to gallstone disease. We were concerned about the possibility that the observed relation between alcohol intake and the risk of cholecystectomy was caused by alcohol avoidance among the women with preclinical gallstone disease. In agreement with this possibility, the association between alcohol intake and the risk of cholecystectomy was slightly weakened when we excluded the first 8 y of follow-up. However, this attenuation may have been due to misclassification of alcohol intake because the women may have changed their alcohol intake after our baseline dietary assessment. Moreover, reverse causation is unlikely to have influenced our results substantially because the inverse associations persisted after we excluded past heavy drinkers, used light alcohol drinkers as the reference group, or excluded women who did not have regular checkups. These 3 steps allowed us to identify the women who, because of early symptoms of gallstone disease, may have consulted their physician more frequently than did the other women.

Measurement error in our assessment of alcohol intake was a potential concern. However, our method of assessing alcohol intake was shown to have a high degree of validity and to be reproducible in a subset from this cohort (38). Moreover, our prospective study design precluded bias attributable to differential recall of alcohol consumption by women who did or did not have a cholecystectomy. Our findings are probably not due to

TABLE 6
Relative risk (RR) of cholecystectomy according to frequency of alcohol intake in 58 374 US women who participated in the Nurses' Health Study (1986–2000) and for whom wine, beer, or liquor was the predominant type of alcoholic beverage consumed[1]

Predominant beverage consumed[2]	No. of cases[3]	No. of person-years	RR (95% CI)	
			Age-adjusted[4]	Multivariate[5]
Wine				
0 d/wk	2702	365 431	Reference	Reference
1–2 d/wk	408	71 560	0.79 (0.71, 0.88)	0.91 (0.82, 1.01)
3–4 d/wk	126	27 535	0.63 (0.53, 0.75)	0.80 (0.67, 0.96)
5–6 d/wk	127	23 819	0.72 (0.61, 0.86)	0.94 (0.78, 1.13)
7 d/wk	92	20 377	0.61 (0.49, 0.75)	0.78 (0.63, 0.97)
Beer				
0 d/wk	2702	365 431	Reference	Reference
1–2 d/wk	100	14 596	0.94 (0.77, 1.15)	0.98 (0.80, 1.20)
3–4 d/wk	38	7404	0.70 (0.51, 0.96)	0.81 (0.59, 1.12)
5–6 d/wk	31	5986	0.70 (0.49, 1.00)	0.80 (0.56, 1.14)
7 d/wk	20	5663	0.47 (0.30, 0.73)	0.57 (0.36, 0.89)
Liquor				
0 d/wk	2702	365 431	Reference	Reference
1–2 d/wk	130	21 133	0.84 (0.71, 1.01)	0.94 (0.79, 1.12)
3–4 d/wk	79	12 670	0.84 (0.67, 1.05)	0.97 (0.77, 1.22)
5–6 d/wk	75	15 348	0.65 (0.52, 0.82)	0.77 (0.61, 0.97)
7 d/wk	97	21 992	0.58 (0.47, 0.71)	0.69 (0.56, 0.86)

[1] The analysis was based on the 1986–2000 follow-up period, so the number of women studied is smaller than that studied during the entire study (ie, from 1980 to 2000). Indicator variables for wine, beer, and liquor consumption were simultaneously entered in the model. The interaction between beverage type and frequency of alcohol intake was not significant.

[2] Defined as the beverage type of which most portions of alcohol were consumed.

[3] Three hundred eleven cases who reported equal consumption of individual alcoholic beverage types were included in the model but are not shown.

[4] RR calculated as the Mantel-Haenszel summary rate ratio, with adjustment for age in 5-y categories.

[5] RR computed by using Cox proportional hazards regression, with adjustment for time period (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), age (<49, 50–54, 55–59, 60–64, ≥65 y), BMI (in kg/m^2) at the beginning of each 2-y follow-up interval (<20.00, 20.00–22.49, 22.50–24.99, 25.00–27.49, 27.50–29.99, 30.00–32.49, 32.50–34.99, 35.00–37.49, 37.50–39.99, ≥40), weight change in the previous 2 y [≥10 lb (4.5 kg) of weight loss, 5.0–9.9 lb (2.25–4.46 kg) of weight loss, maintained weight ± 4.9 lb (2.2 kg), 5.0–9.9 lb (2.25–4.46 kg) of weight gain, ≥10 lb (4.5 kg) of weight gain], parity (0, 1, 2–3, ≥4 births), oral contraceptive use (ever or never), hormone replacement therapy (premenopausal, postmenopausal without hormone replacement therapy, postmenopausal with past hormone replacement therapy, and postmenopausal with current hormone replacement therapy), physical activity (quintiles), history of diabetes mellitus (yes or no), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, ≥65), use of thiazide diuretics (yes or no), energy-adjusted fiber intake (quintiles), energy-adjusted carbohydrate intake (quintiles), energy-adjusted polyunsaturated fat intake (quintiles), and coffee intake (0, 1, 2–3, ≥4 cups/d; 1 cup = 237 mL).

underascertainment of cholecystectomy cases, because this circumstance would not have biased the observed RRs (41).

Alcohol consumption may decrease the risk of gallstone disease by affecting bile lithogenicity. The decrease in cholesterol saturation index observed with moderate alcohol intakes (42) may be due to an increased conversion of cholesterol to bile acids (43) and a decreased ratio of trihydroxy to dihydroxy bile acids (44). Serum HDL-cholesterol concentrations, which correlate directly with total biliary bile acids (45), are elevated in persons who regularly consume alcohol (46) and are inversely associated with bile lithogenicity (47) and the prevalence of gallstones (10). Whereas regular alcohol intake increases serum HDL, binge drinking has little effect on serum HDL concentrations (48).

Alternatively, alcohol consumption may confer protection against gallstone development by stimulating gallbladder emptying and accelerating gallbladder filling (49). These effects could be mediated by the effect of alcohol on gallbladder membrane transport properties. Alcohol reduces bile concentrations by inhibiting the absorption of water and electrolytes by the gallbladder mucosa (50). These mechanisms are likely to operate better with frequent than with infrequent alcohol consumption. Another possibility is that alcohol exerts a prokinetic effect on the gut (51). Gallstone formation is favored by decreased intestinal transit mainly because of increased colonic absorption of deoxycholic acid (52), which is known to promote cholesterol nucleation (53).

In conclusion, our findings suggest that frequent, moderate alcohol intake is associated with a decreased risk of cholecystectomy in women. All types of alcoholic beverages were inversely associated with the risk of cholecystectomy. Despite the inverse association between regular, moderate alcohol intake and gallstone disease, interested patients should discuss the health effects of alcohol consumption with their health care providers, who can help determine the patients' overall health risks and benefits, as well as provide an individual clinical recommendation.

We are indebted to the participants in the Nurses' Health Study for their continuing cooperation and to Gary Chase, Karen Corsano, Lisa Dunn, Barbara Egan, Lori Ward, Mary Louie, and Laura Sampson for expert help.

MFL, C-JT, MJS, EBR, GAC, WCW, and ELG contributed to the study concept and design, the acquisition of data, the analysis and interpretation of data, the drafting of the manuscript, the critical revision of the manuscript for important intellectual content, and the statistical analysis. Funding was obtained by EBR, GAC, and WCW. Administrative, technical, or material support was provided by MJS, EBR, GAC, WCW, and ELG. None of the authors had any conflict of interest in connection with this article.

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