Frequent nut consumption and decreased risk of cholecystectomy in women[1–3]

Chung-Jyi Tsai, Michael F Leitzmann, Frank B Hu, Walter C Willett, and Edward L Giovannucci

ABSTRACT

Background: Gallstone disease is a major source of morbidity in the developed countries. Nuts are rich in several compounds that may protect against gallstone disease.

Objective: The association between nut intake and cholecystectomy was examined in a large cohort of women.

Design: We prospectively studied nut (peanuts, other nuts, and peanut butter) consumption in relation to the risk of cholecystectomy in a cohort of 80 718 women from the Nurses' Health Study who were 30–55 y old in 1980 and had no history of gallstone disease. As part of the Nurses' Health Study, the women reported on questionnaires mailed to them every 2 y both their consumption of nuts and whether they had undergone cholecystectomy. The women were followed through 2000.

Results: During 1 393 256 person-years of follow-up from 1980 to 2000, we documented 7831 cholecystectomies. After adjustment for age and other known or suspected risk factors, women who consumed ≥5 units of nuts (1 unit = 1 oz or 28.6 g nuts)/wk (frequent consumption) had a significantly lower risk of cholecystectomy (relative risk: 0.75; 95% CI: 0.66, 0.85; *P* for trend < 0.0001) than did women who never ate nuts or who ate <1 unit/mo (rare consumption). Further adjustment for fat consumption (saturated fat, *trans* fat, polyunsaturated fat, and monounsaturated fat) did not materially alter the relation. In analyses examining consumption of peanuts and other nuts separately, both were associated with a lower risk of cholecystectomy.

Conclusion: In women, frequent nut consumption is associated with a reduced risk of cholecystectomy. *Am J Clin Nutr* 2004;80: 76–81.

KEY WORDS Nuts, gallstones, cholecystectomy, prospective study, women

INTRODUCTION

Gallbladder disease is common among adults in the United States and Western countries and is a major source of abdominal morbidity (1, 2). Most of the studies on the relation between diet and gallstone disease have considered the intakes of various nutrients (3–5). Little attention has been paid to the effect of specific foods. The influence of any particular food may depend on its unique combination of complex chemicals.

In most Western populations, an estimated 80% of gallstones are cholesterol stones. The imbalance between secretion of cholesterol and secretion of bile acids and phospholipids into the biliary tree is an important determinant of the formation of cholesterol gallstones (6). High plasma triacylglycerol concentrations and low plasma HDL-cholesterol concentrations are associated with the risk of developing gallstones (6–13). Nuts are rich in several compounds that have beneficial effects on blood cholesterol and lipoprotein profiles (14–16); most of the fats in nuts are unsaturated fats (17–19), and the amount of saturated fat is relatively small. In animal studies, these dietary lipid profiles may reduce the occurrence of gallstones (20, 21). Nuts are also a rich source of dietary fiber (19), which may be beneficial in preventing gallstone disease. However, the relation between nut consumption and gallstone disease has hardly been evaluated. To address this, we prospectively examined nut consumption in relation to the risk of cholecystectomy in a cohort of women in the United States.

SUBJECTS AND METHODS

Study population

In the Nurses' Health Study, 121 700 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 follow-up of 80 718 women who answered the 1980 dietary questionnaire, did not have a cholecystectomy or a gallstone diagnosis before 1980, did not have diagnosed cancer at baseline, and provided adequate dietary data. 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 nut consumption

In 1980 a dietary questionnaire comprising 61 items was included as part of the follow-up questionnaire. In 1984 the dietary questionnaire was expanded to include 116 items. Similar questionnaires

[1] From the Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, and the Department of Nutrition, Harvard School of Public Health, Boston.

[2] Supported by research grants (CA55075 and DK46200) from the National Institutes of Health.

[3] Reprints not available. Address correspondence to C-J Tsai, Center for Digestive Diseases, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242. E-mail: hpcjt@channing.harvard.edu.

Received August 29, 2003.
Accepted for publication January 5, 2004.

were used to update information on the subjects' diet in 1986, 1990, 1994, and 1998. In the 1980 and 1984 questionnaires, participants were asked to report their average nut consumption (1 unit = 1 oz or 28.6 g nuts) over the past year with the use of 9 prespecified responses ranging from never or almost never to ≥6 times/d. In the 1986, 1990, 1994, and 1998 dietary questionnaires, the question was split into 2 items concerning the consumption of peanuts, which are not botanically nuts, and the consumption of other nuts. Thus, the data on total consumption of nuts in 1986, 1990, 1994, and 1998 came from these 2 items combined. Because the separate intakes of peanuts and other nuts were first reported in 1986, in the analyses involving these food items, we began follow-up in 1986 and excluded women who had a cholecystectomy or diagnosis of gallbladder disease before the return of the 1986 questionnaire. Our assessment of nut consumption also included information on peanut butter (1 tbsp = 1 oz or 28.6 g peanuts). In a validation study in a random sample of 173 participants from the Boston area, the correlation coefficient between the intake of nuts assessed by using the 1980 questionnaire and that assessed by using multiple-week dietary records was 0.66 (22).

Identification of cholecystectomy cases

We inquired about the occurrence and the 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 the 50 participants responded. Of these 43 participants, all reiterated their earlier report, and 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 of untreated gallstones. In addition, symptomatic gallstones are the main indication for cholecystectomy. In contrast, only a minor proportion of asymptomatic gallstones are diagnosed, typically incidentally, which makes this clinically less relevant condition an unreliable endpoint. In our cohort, 80% of the women who had a cholecystectomy between 1980 and 1986 reported a diagnosis of symptomatic gallstone disease, and only 12% of the women who reported a diagnosis of gallstones with accompanying symptoms between 1980 and 1986 did not have a cholecystectomy during that time period.

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, or last questionnaire return; death; or the end of the study period in 2000, whichever came first. Women were divided into 5 categories according to their nut consumption: <1 time/mo, 1–3 times/mo, 1 time/wk, 2–4 times/wk, and ≥5 times/wk. 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 nut consumption divided by the incidence rate in the lowest category of nut consumption, with adjustment for age in 5-y categories.

Multivariate relative risks were computed by using the Cox proportional hazards regression model (24). In multivariate analyses, we simultaneously adjusted for the following known or suspected confounding variables: time period, age, body mass index, weight change in the previous interval, physical activity, parity, oral contraceptive use, postmenopausal hormone use, history of diabetes mellitus, pack-years of smoking, use of thiazide diuretics, use of nonsteroidal antiinflammatory drugs, total energy intake, energy-adjusted dietary fiber intake, energy-adjusted carbohydrate intake, alcohol intake, and coffee intake. These variables were chosen because they have been found to be related both to nut consumption and to the risk of developing gallstones and thus represent potentially confounding variables in the relation between nuts and cholecystectomies. Tests of linear trend across increasing categories of nut intake were conducted by assigning the median nut intake for each intake category and treating these median values as a single continuous variable.

To account for changes in nut intake over time, we conducted our primary analyses by using cumulative averaged intakes of nuts. In alternative analyses, we analyzed the incidence of cholecystectomy in relation to nut intake at baseline. We conducted various analyses to address the possibility that underlying symptoms related to cholecystectomy caused a change in nut consumption, which thereby biased our results by creating spurious associations. All relative risks 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, ≈29.6% of the participants reported eating 1 unit of nuts (equivalent to 1 oz or 28.6 g nuts) ≥1 time/wk. Among all the participants, 5.3% reported eating nuts ≥5 times/wk, 9.2% reported eating nuts 2–4 times/wk, and 15.1% reported eating nuts 1 time/wk. Compared with the women who rarely consumed nuts in 1980, those who consumed nuts frequently tended to be more physically active, to be thinner, to be less likely to smoke, and to drink more alcohol but less coffee (**Table 1**). Frequent nut consumption was associated with a lower intake of carbohydrate and higher intakes of polyunsaturated fat and fiber.

During 1 393 256 person-years of follow-up from 1980 to 2000, we documented 7831 cases of cholecystectomy. The relative risk for the women who consumed nuts ≥5 times/wk compared with those who rarely consumed nuts was 0.66 (95% CI: 0.58, 0.74; *P* for trend < 0.0001) in the age-adjusted analysis and was slightly attenuated after adjustment for multiple potential confounding variables (relative risk: 0.75; 95% CI: 0.66, 0.85; *P* for trend < 0.0001) (**Table 2**). After further adjustment for intakes of saturated fat, polyunsaturated fat, *trans* fat, and monounsaturated fat, the relative risk of cholecystectomy from consuming nuts ≥5 times/wk was 0.78 (95% CI: 0.68, 0.88; *P* for trend < 0.0001). To address the effect of long-term nut consumption, we evaluated the association between the baseline intake of nuts and the risk of cholecystectomy. Similar associations were observed. The multivariate relative risk among the women who consumed nuts ≥5 times/wk compared with those who rarely ate nuts was 0.85 (95% CI: 0.74, 0.96; *P* for trend = 0.0009).

To examine the possibility that latent gallstone symptoms caused a decrease in nut consumption, which thereby biased the results, we conducted analyses in which all cases that occurred during the first 2-y and 4-y follow-up periods were excluded to address the concern of any potential change in diet due to preclinical conditions. Compared with the women who rarely consumed nuts, those who ate nuts ≥5 times/wk had multivariate

TABLE 1
Baseline characteristics according to frequency of total nut consumption among women in the Nurses' Health Study[1]

Characteristic	Frequency of total nut consumption: <1 time/mo (*n* = 27 678)	1–3 times/mo (*n* = 29 335)	1 time/wk (*n* = 12 178)	2–4 times/wk (*n* = 7428)	≥5 times/wk (*n* = 4279)	*P* for trend
Nut intake (servings/d)[2]	0	0.07	0.14	0.33	0.79	< 0.0001
Age (y)	46.0 ± 7.2[3]	45.7 ± 7.2	45.9 ± 7.1	46.7 ± 7.2	47.5 ± 7.1	< 0.0001
Current BMI (kg/m^2)	24.5 ± 4.5	24.1 ± 4.3	24.0 ± 4.1	23.7 ± 3.9	23.4 ± 3.8	< 0.0001
Any weight loss in prior 2 y (%)	30.9	28.8	28.1	28.9	30.4	0.0006
History of oral contraceptive use (%)	48.6	50.1	50.1	51.8	49.8	< 0.0001
Current use of HRT (%)	14.2	14.3	14.6	15.5	15.4	< 0.0001
Current smoker (%)	32.0	27.8	26.0	25.4	24.8	< 0.0001
History of diabetes (%)	2.5	1.7	1.8	1.7	2.3	< 0.0001
Regular use of aspirin (%)	46.2	47.0	47.6	45.3	43.8	0.02
Regular use of thiazide diuretics (%)	10.8	9.7	8.3	9.0	7.9	< 0.0001
Physical activity (h/wk)	2.7 ± 2.4	3.0 ± 2.5	3.2 ± 2.6	3.4 ± 2.7	3.4 ± 2.7	< 0.0001
Daily intake						
Dietary fiber (g)[4]	13.2 ± 4.9	13.3 ± 4.5	13.9 ± 4.5	14.9 ± 4.9	16.2 ± 4.9	< 0.0001
Polyunsaturated fat (g)[4]	8.7 ± 2.8	9.3 ± 2.6	9.5 ± 2.5	10.2 ± 2.5	12.0 ± 3.2	< 0.0001
Carbohydrate (g)[4]	157 ± 38	155 ± 36	155 ± 35	153 ± 35	148 ± 38	< 0.0001
Alcohol (g)	5.9 ± 10.6	6.3 ± 10.3	7.1 ± 10.5	7.6 ± 11.1	7.9 ± 12.1	< 0.0001
Coffee (cups)	2.3 ± 2.1	2.3 ± 2.0	2.3 ± 2.0	2.2 ± 2.0	2.1 ± 2.1	< 0.0001

[1] HRT, hormone replacement therapy among the subset of total study participants who were postmenopausal. 1 cup coffee = 237 mL.
[2] Median.
[3] $\bar{x}$ ± SD (all such values).
[4] Adjusted for total energy intake.

relative risks of cholecystectomy of 0.84 (95% CI: 0.73, 0.96; *P* for trend = 0.002) and 0.85 (95% CI: 0.74, 0.97; *P* for trend = 0.005) after exclusion of the first 2-y and 4-y follow-up periods, respectively.

In separate analyses, we examined individual consumption of peanuts, peanut butter, and other nuts. Comparing consumption of ≥5 times/wk with consumption of <1 time/mo, the multivariate relative risks were 0.81 (95% CI: 0.64, 1.01; *P* for trend = 0.02) for peanuts, 0.85 (95% CI: 0.78, 0.93; *P* for trend = 0.001) for peanut butter, and 0.65 (95% CI: 0.46, 0.93; *P* for trend = 0.005) for other nuts. All these associations with the risk of cholecystectomy were only slightly weakened after further

TABLE 2
Relative risks (RRs) of cholecystectomy according to frequency of total nut consumption among US women in the Nurses' Health Study[1]

Variable	Frequency of total nut consumption: <1 time/mo	1–3 times/mo	1 time/wk	2–4 times/wk	≥5 times/wk	*P* for trend
Cases (*n*)	2236	3058	916	1308	313	
Person-years	359 791	541 106	140 054	279 607	72 699	
RR						
Model 1[2]	1.0	0.90 (0.85, 0.95)	0.98 (0.90, 1.06)	0.74 (0.69, 0.80)	0.66 (0.58, 0.74)	<0.0001
Model 2[3]	1.0	0.89 (0.84, 0.94)	0.91 (0.84, 0.99)	0.79 (0.74, 0.86)	0.75 (0.66, 0.85)	<0.0001
Model 3[4]	1.0	0.89 (0.84, 0.94)	0.92 (0.85, 0.99)	0.81 (0.75, 0.87)	0.78 (0.68, 0.88)	<0.0001

[1] 95% CIs in parentheses. 1 lb = 0.45 kg. 1 cup coffee = 237 mL.
[2] Adjustment for age (5-y categories).
[3] Adjustment for age (1-y categories), time period (1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), 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 of weight loss, 5.0–9.9 lb of weight loss, maintained weight ± 4.9 lb, 5.0–9.9 lb of weight gain, ≥10 lb 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), use of nonsteroidal antiinflammatory drugs (0, 1–6, ≥7 times/wk, and dose unknown), total energy intake (quintiles), energy-adjusted dietary fiber intake (quintiles), energy-adjusted carbohydrate intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0 g/d), and coffee intake (0, 1, 2–3, ≥4 cups/d).
[4] Adjustment for all the covariates in model 2 plus additional adjustment for quintiles of intake of saturated fat, *trans* fat, polyunsaturated fat, and monounsaturated fat.

TABLE 3
Relative risks (RRs) of cholecystectomy according to frequency of consumption of peanuts, peanut butter, and other nuts among US women in the Nurses' Health Study[1]

	Frequency of consumption					
Variable	<1 time/mo	1–3 times/mo	1 time/wk	2–4 times/wk	≥5 times/wk	*P* for trend
Peanuts						
Cases (*n*)	1776	1829	342	607	82	
Person-years	264 333	264 289	48 076	105 744	16 840	
RR						
Model 1[2]	1.0	1.01 (0.95, 1.08)	1.02 (0.90, 1.14)	0.84 (0.77, 0.93)	0.70 (0.56, 0.87)	<0.0001
Model 2[3]	1.0	0.97 (0.90, 1.04)	0.96 (0.85, 1.08)	0.92 (0.83, 1.01)	0.81 (0.64, 1.01)	0.02
Model 3[4]	1.0	0.97 (0.91, 1.04)	0.97 (0.86, 1.09)	0.94 (0.85, 1.04)	0.84 (0.67, 1.07)	0.09
Peanut butter						
Cases (*n*)	1602	2178	880	2422	749	
Person-years	322 420	364 962	140 922	413 957	150 996	
RR						
Model 1[2]	1.0	1.15 (1.07, 1.22)	1.16 (1.07, 1.26)	1.13 (1.06, 1.20)	0.95 (0.87, 1.04)	0.05
Model 2[3]	1.0	1.00 (0.94, 1.07)	0.92 (0.84, 1.00)	0.98 (0.92, 1.05)	0.85 (0.78, 0.93)	0.001
Model 3[4]	1.0	1.00 (0.94, 1.07)	0.92 (0.84, 1.01)	0.99 (0.93, 1.06)	0.88 (0.79, 0.96)	0.01
Other nuts						
Cases (*n*)	2191	1751	264	398	32	
Person-years	327 448	256 547	36 964	69 904	8420	
RR						
Model 1[2]	1.0	0.99 (0.93, 1.05)	1.01 (0.89, 1.15)	0.83 (0.75, 0.93)	0.54 (0.38, 0.77)	<0.0001
Model 2[3]	1.0	0.95 (0.89, 1.02)	0.97 (0.85, 1.11)	0.81 (0.81, 1.01)	0.65 (0.46, 0.93)	0.005
Model 3[4]	1.0	0.96 (0.90, 1.03)	0.99 (0.87, 1.14)	0.93 (0.83, 1.04)	0.69 (0.48, 0.99)	0.04

[1] 95% CIs in parentheses. The analyses of peanuts and other nuts were based on the 1986–2000 follow-up period, so the number of women studied is smaller than that for the other analyses (ie, the analyses of total nut consumption).
[2] Adjustment for age (5-y categories).
[3] Adjustment for the same covariates listed for model 2 in Table 2.
[4] Adjustment for all the covariates in model 2 plus additional adjustment for quintiles of intake of saturated fat, *trans* fat, polyunsaturated fat, and monounsaturated fat.

adjustment for intakes of saturated fat, polyunsaturated fat, *trans* fat, and monounsaturated fat (**Table 3**).

DISCUSSION

We found a significant inverse association between nut consumption and the risk of cholecystectomy in this large prospective cohort study of women. Our data suggest an apparent threshold effect, with reduction in the risk of cholecystectomy observed only with relatively frequent nut consumption. We evaluated whether confounding could explain the observed inverse association because women who frequently consumed nuts tended to have dietary or behavioral factors that could protect against gallstone disease. Adjustments for these variables only slightly attenuated the associations, and a clear, significant risk reduction persisted in multivariate analyses. Although the extensive information on multiple risk factors enabled us to adjust for known confounding variables, the possibility of residual confounding attributable to unmeasured dietary, behavioral, or genetic factors could not be completely excluded. Nevertheless, residual confounding probably could not fully explain the robust observed inverse relation (25).

The relation between nut intake and gallstone disease has hardly been studied despite the biological plausibility that nut consumption may reduce the risk. A reduction in serum lipid concentrations by various nuts or peanuts has been shown in several well-controlled clinical studies (26–29). Because the major source of energy in nuts is fat, the beneficial effects on blood lipids that are ascribed to nuts may be due to their high content of unsaturated fatty acids and low content of saturated and *trans* fatty acids (30, 31). Monounsaturated and polyunsaturated fats may act as inhibitors of cholesterol cholelithiasis and hence may protect against cholesterol gallstone disease (20, 21, 32). Probably because different types of nuts are made up of similar nutrients, including fatty acids (31), there were similar inverse relations of peanuts and other nuts with the risk of cholecystectomy in the present study.

Because of their high fat content, nuts are traditionally included among foods to be avoided, and there may be a concern that higher nut consumption could result in weight gain and might therefore increase the risk of developing gallstones. However, in our cohort, the women who consumed more nuts tended to weigh less. This indicates that the energy contained in nuts tends to be balanced by decreased intakes of other sources of energy or by increased physical activity.

As a complex plant food, nuts contain many nutrients and other bioactive compounds (33). Because an inverse association persisted after control for the intakes of specific fatty acids, the reduction in the risk of cholecystectomy is probably not explained solely by the fatty acid profile of nuts. Other bioactive components that further reduce the risk may be present in nuts. Nuts are a rich source of dietary fiber. One ounce (28 g) of peanuts or mixed nuts provides 2.4–2.6 g dietary fiber. Dietary fiber may protect against cholesterol gallstone formation by decreasing recirculation of secondary bile acids in the intestine and by improving insulin sensitivity (34–36). Nuts are also a source of phytosterols, which may lower blood cholesterol by inhibiting dietary cholesterol absorption (37) and thus might contribute to the reduced risk of developing gallstones. Nuts are also a rich source of magnesium. Dietary magnesium has been suggested to play a role in improving insulin sensitivity and hence may decrease the occurrence of gallstones (38–40).

The possibility of misclassification might be of concern because information on nut consumption was collected by self-report. However, nut consumption was reported on dietary questionnaires with reasonable accuracy (22). Moreover, we assessed nut consumption repeatedly during the successive follow-up periods, and the updated analyses took into consideration any potential dietary changes over time. Because the data regarding nut consumption were collected before the diagnosis of gallstone disease, any misclassification would be nondifferential between cases and noncases and would most likely weaken any true relation.

We could not exclude the possibility that participants with latent gallstone disease may have decreased their nut consumption because of abdominal symptoms. Consequently, those participants may have consulted physicians frequently, which may have increased the detection rate of gallstone disease. However, the magnitude of this bias would have to be quite substantial to account entirely for the observed inverse relation. Moreover, after exclusion of the first 2 and 4 y of follow-up, the inverse association persisted. In conclusion, our findings suggest that frequent nut consumption is associated with a reduced risk of cholecystectomy in women.

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

All authors contributed to the study concept and design, the acquisition of data, the analysis and interpretation of data, the drafting of the manuscript, and the statistical analysis. Funding was obtained by WCW, FBH, and ELG. None of the authors had any conflicts of interest in connection with this article.

REFERENCES

1. Kang JY, Ellis C, Majeed A, et al. Gallstones—an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. Aliment Pharmacol Ther 2003;17:561–9.
2. National Hospital Discharge Survey: 2000 annual summary with detailed diagnosis and procedure data. Vital Health Stat 13 2003:153.
3. Kratzer W, Kachele V, Mason RA, et al. Gallstone prevalence in relation to smoking, alcohol, coffee consumption, and nutrition: the Ulm Gallstone Study. Scand J Gastroenterol 1997;32:953–8.
4. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Willett WC. Dietary predictors of symptom-associated gallstones in middle-aged women. Am J Clin Nutr 1990;52:916–22.
5. Leitzmann MF, Willett WC, Rimm EB, et al. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. JAMA 1999;281:2106–12.
6. Cohen DE. Pathogenesis of gallstones. In: Zakim D, Boyer TD, eds. Hepatology: a textbook of liver disease. 4th ed. Philadelphia: WB Saunders, 2003:1713–43.
7. Dowling RH. Pathogenesis of gallstones. Aliment Pharmacol Ther 2000;14(suppl):39–47.
8. Attili AF, Capocaccia R, Carulli N, et al. Factors associated with gallstone disease in the MICOL experience. Hepatology 1997;26:809–18.
9. Petiti DB, Friedman GD, Klatsky AL. Association of a history of a gallbladder disease with a reduced concentration of high-density-lipoprotein cholesterol. N Engl J Med 1981;23:1396–8.
10. Thijs C, Knipschild P, Brombacher P. Serum lipids and gallstones: a case-control study. Gastroenterology 1990;99:843–9.
11. Diehl AK, Haffner SM, Hazuda HP, Stern MP. Coronary risk factors and clinical gallbladder disease: an approach to the prevention of gallstones? Am J Public Health 1987;77:841–5.
12. Fuchs M, Ivandic B, Muller O, et al. Biliary cholesterol hypersecretion in gallstone-susceptible mice is associated with hepatic up-regulation of the high-density lipoprotein receptor SRBI. Hepatology 2001;33:1451–9.
13. Laakso M, Suhonen M, Julkunen R, Pyorala K. Plasma insulin, serum lipids and lipoproteins in gallstone disease in non-insulin dependent diabetic subjects: a case control study. Gut 1990;31:344–7.
14. Abbey M, Noakes M, Belling GB, Nestel PJ. Partial replacement of saturated fatty acids with almonds or walnuts lowers total plasma cholesterol and low-density-lipoprotein cholesterol. Am J Clin Nutr 1994;59:995–9.
15. Sabate J, Fraser GE, Burke K, Knutsen SF, Bennett H, Lindsted KD. Effect of walnuts on serum lipid levels and blood pressure in normal men. N Engl J Med 1993;328:603–7.
16. Almario RU, Vonghavaravat V, Wong R, Kasim-Karakas SE. Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. Am J Clin Nutr 2001;74:72–9.
17. Rajaram S, Burke K, Connell B, Myint T, Sabate J. A monounsaturated fatty acid–rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women. J Nutr 2001;131:2275–9.
18. Spiller GA, Jenkins DAJ, Bosello O, Gates JE, Cragen LN, Bruce B. Nuts and plasma lipids: an almond-based diet lowers LDL-C while preserving HDL-C. J Am Coll Nutr 1998;17:285–90.
19. Kris-Etherton PM, Zhao G, Binkoski AE, Coval SM, Etherton TD. The effects of nuts on coronary heart disease risk. Nutr Rev 2001;59:103–11.
20. Cohen BI, Mosbach EH, Ayyad N, Miki S, McSherry CK. Dietary fat and fatty acids modulate cholesterol cholelithiasis in the hamster. Lipids 1992;27:526–32.
21. Ayyad N, Cohen BI, Ohshima A, Mosbach EH. Prevention of cholesterol cholelithiasis by dietary unsaturated fats in hormone-treated female hamsters. Lipids 1996;31:721–7.
22. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
23. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med 1989;321:563–9.
24. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
25. Flanders WD, Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. Epidemiology 1990;1:239–46.
26. Zambon D, Sabate J, Munoz S, et al. Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women. Ann Intern Med 2000;132:538–46.
27. Morgan WA, Clayshulte BJ. Pecans lower low-density lipoprotein cholesterol in people with normal lipid levels. J Am Diet Assoc 2000;100:312–8.
28. Curb JD, Wergowske G, Dobbs JC, Abbott RD, Huang B. Serum lipid effects of a high-monounsaturated fat diet based on macadamia nuts. Arch Intern Med 2000;160:1154–8.
29. Edwards D, Kwaw I, Matud J, Kurtz I. Effect of pistachio nuts on serum lipid levels in patients with moderate hypercholesterolemia. J Am Coll Nutr 1999;18:229–32.
30. Grundy SM, Denke MA. Dietary influences on serum lipids and lipoproteins. J Lipid Res 1990;31:1149–72.
31. Dreher ML, Maher CV. The traditional and emerging role of nuts in healthful diets. Nutr Rev 1996;54:241–5.
32. Jonnalagadda SS, Trautwein EA, Hayes KC. Dietary fats rich in saturated fatty acids (12:0, 14:0, and 16:0) enhance gallstone formation relative to monounsaturated fat (18:1) in cholesterol-fed hamsters. Lipids 1995;30:415–24.
33. Kris-Etherton PM, Yu-Poth S, Sabate J, Ratcliffe HE, Zhao G, Etherton TD. Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. Am J Clin Nutr 1999;70(suppl):504S–11S.
34. Schwesinger WH, Kurtin WE, Page CP, Stewart RM, Johnson R. Soluble dietary fiber protects against cholesterol gallstone formation. Am J Surg 1999;177:307–10.

35. Misciagna G, Centonze S, Leoci C, et al. Diet, physical activity, and gallstones—a population-based, case-control study in southern Italy. Am J Clin Nutr 1999;69:120–6.
36. Sichieri R, Everhart JE, Roth H. A prospective study of hospitalization with gallstone disease among women: role of dietary factors, fasting period, and dieting. Am J Public Health 1991;81:880–4.
37. Jones PJ, MacDougall DE, Ntanios F, Vanstone CA. Dietary phytosterols as cholesterol-lowering agents in humans. Can J Physiol Pharmacol 1997;75:217–27.
38. Humphries S, Kushner H, Falkner B. Low dietary magnesium is associated with insulin resistance in a sample of young, nondiabetic Black Americans. Am J Hypertens 1999;12:747–56.
39. Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. Hepatology 2000;31:299–303.
40. Dubrac S, Parquet M, Blouquit Y, et al. Insulin injections enhance cholesterol gallstone incidence by changing the biliary cholesterol saturation index and apo A-I concentration in hamsters fed a lithogenic diet. J Hepatol 2001;35:550–7.