

# Frequent nut consumption and decreased risk of cholecystectomy in women<sup>1-3</sup>

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## 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  $\geq 5$  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

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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  $\geq 6$  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  $\geq 5$  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,  $\approx 29.6\%$  of the participants reported eating 1 unit of nuts (equivalent to 1 oz or 28.6 g nuts)  $\geq 1$  time/wk. Among all the participants, 5.3% reported eating nuts  $\geq 5$  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  $\geq 5$  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  $\geq 5$  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  $\geq 5$  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 pre-clinical conditions. Compared with the women who rarely consumed nuts, those who ate nuts  $\geq 5$  times/wk had multivariate



**TABLE 1**Baseline characteristics according to frequency of total nut consumption among women in the Nurses' Health Study<sup>1</sup>

Characteristic	Frequency of total nut consumption					P for trend
	<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)	
Nut intake (servings/d) <sup>2</sup>	0	0.07	0.14	0.33	0.79	< 0.0001
Age (y)	46.0 ± 7.2 <sup>3</sup>	45.7 ± 7.2	45.9 ± 7.1	46.7 ± 7.2	47.5 ± 7.1	< 0.0001
Current BMI (kg/m <sup>2</sup> )	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) <sup>4</sup>	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) <sup>4</sup>	8.7 ± 2.8	9.3 ± 2.6	9.5 ± 2.5	10.2 ± 2.5	12.0 ± 3.2	< 0.0001
Carbohydrate (g) <sup>4</sup>	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

<sup>1</sup> HRT, hormone replacement therapy among the subset of total study participants who were postmenopausal. 1 cup coffee = 237 mL.<sup>2</sup> Median.<sup>3</sup>  $\bar{x} \pm SD$  (all such values).<sup>4</sup> 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<sup>1</sup>

Variable	Frequency of total nut consumption					P for trend
	<1 time/mo	1–3 times/mo	1 time/wk	2–4 times/wk	≥5 times/wk	
Cases (n)	2236	3058	916	1308	313	
Person-years	359 791	541 106	140 054	279 607	72 699	
RR						
Model 1 <sup>2</sup>	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 <sup>3</sup>	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 <sup>4</sup>	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

<sup>1</sup> 95% CIs in parentheses. 1 lb = 0.45 kg. 1 cup coffee = 237 mL.<sup>2</sup> Adjustment for age (5-y categories).

<sup>3</sup> 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<sup>2</sup>) 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).

<sup>4</sup> 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<sup>1</sup>

Variable	Frequency of consumption					P for trend
	<1 time/mo	1–3 times/mo	1 time/wk	2–4 times/wk	≥5 times/wk	
<b>Peanuts</b>						
Cases ( <i>n</i> )	1776	1829	342	607	82	
Person-years	264 333	264 289	48 076	105 744	16 840	
RR						
Model 1 <sup>2</sup>	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 <sup>3</sup>	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 <sup>4</sup>	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
<b>Peanut butter</b>						
Cases ( <i>n</i> )	1602	2178	880	2422	749	
Person-years	322 420	364 962	140 922	413 957	150 996	
RR						
Model 1 <sup>2</sup>	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 <sup>3</sup>	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 <sup>4</sup>	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
<b>Other nuts</b>						
Cases ( <i>n</i> )	2191	1751	264	398	32	
Person-years	327 448	256 547	36 964	69 904	8420	
RR						
Model 1 <sup>2</sup>	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 <sup>3</sup>	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 <sup>4</sup>	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

<sup>1</sup> 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).

<sup>2</sup> Adjustment for age (5-y categories).

<sup>3</sup> Adjustment for the same covariates listed for model 2 in Table 2.

<sup>4</sup> 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. 

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