Long-Term Intake of Dietary Fiber and Decreased Risk of Cholecystectomy in Women

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BACKGROUND: Epidemiologic studies on the relationship between dietary fiber and gallstone disease are inconclusive, and the effects of different types of dietary fiber are not clear.

METHODS: We examined the association between long-term intake of dietary fiber as well as fiber from different sources and risk of cholecystectomy in a cohort of 69,778 women who were aged from 35 to 61 years in 1984 and had no history of gallstone disease. As part of the Nurses' Health Study, the women reported on questionnaires mailed to them every two years both their fiber intake and whether they had undergone cholecystectomy.

RESULTS: During 16 yr of follow-up, we documented 5,771 cases of cholecystectomy. After adjusting for age and other known or suspected risk factors in a multivariate model, compared with women in the lowest quintile of total dietary fiber intake, the relative risk of choleystectomy for those in the highest quintile was 0.87 (95% CI, 0.78–0.96, p for trend = 0.005). For a 5-g increase in total fiber intake, the multivariate relative risk was 0.94 (95% CI, 0.90–0.98). Insoluble fiber, taking soluble fiber into account in the multivariate model, was significantly associated with a reduced risk. The multivariate relative risk was 0.83 (95% CI, 0.73–0.94, p for trend = 0.009) for insoluble fiber, and was 1.01 (95% CI, 0.89–1.15, p for trend = 0.9) for soluble fiber, when extreme quintiles were compared. For a 5-g increase in intake, the relative risk was 0.90 (95% CI, 0.84–0.97) for insoluble fiber, and was 1.01 (95% CI, 0.83–1.23) for soluble fiber.

CONCLUSIONS: Our results suggest that increased long-term consumption of dietary fiber, particularly insoluble fiber, can reduce risk of cholecystectomy in women.

INTRODUCTION

Gallstone disease is a common condition of adults in the United States and other developed countries (1), and is increasingly becoming a major cause of abdominal morbidity leading to hospital admission (2, 3). Among western countries, an estimated 80% of gallstones are cholesterol stones (4). Cholesterol gallstones have many causative factors, but biliary hypersecretion of cholesterol is an important determinant (4). Low plasma high-density lipoprotein (HDL) cholesterol and high plasma triglyceride levels are associated with greater risk for gallstones (4, 5), and hyperinsulinemia may enhance gallstone development (6, 7).

High intake of dietary fiber may protect against gallstone disease because it can lower serum triglyceride levels and increase insulin sensitivity (8–10). In addition, fiber may speed intestinal transit and reduce the generation of secondary bile acids, which have been associated with increased cholesterol saturation of the bile (11, 12). Several studies have examined dietary fiber in relation to gallstone disease, but results

have been divergent (13–17). These studies have been limited by small numbers, incomplete dietary measures, or short-term dietary assessment. Although the physiological consequences of a high-fiber diet may depend on the type and source of fiber, intakes of specific types, and sources of dietary fiber have been little studied in relation to the occurrence of gallstones.

To address these issues, we examined in detail the relation between intake of dietary fiber and risk of cholecystectomy in the Nurses' Health Study, a large, prospective cohort of women. Estimates of fiber intake were based on repeated dietary measurements during 16 yr of follow-up, thus providing a measure of long-term consumption of dietary fiber.

METHODS

Study Population

The Nurses' Health Study was initiated in 1976 when 121,700 female registered nurses, predominantly Caucasian, aged

30–55 yr completed a mailed questionnaire on their medical history and lifestyle characteristics. Every 2-yr, follow-up questionnaires were sent to update information on exposures and to identify newly diagnosed illnesses. In 1984, we collected dietary information with a 116-item semiquantitative food-frequency questionnaire (SFFQ) that included details for assessing sources of fiber intake. A total of 81,757 women returned the SFFQ and satisfied *a priori* criteria of daily energy intakes between 600 and 3,500 kcal. We further excluded women with 11 or more blank food questionnaire items, or prior diagnosis of gallstone disease or cancer. The final baseline population was 69,778 women aged 35–61 yr in 1984. On average, more than 90% responded to each subsequent biennial questionnaire, and about 80% completed each repeated dietary questionnaire during the follow-up. 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 Diet

Dietary information was derived from an SFFQ (18) administered in 1984, 1986, 1990, 1994, and 1998. Participants were asked to indicate the frequency, on average, of consuming a typical serving of selected foods during the previous year. There were nine possible response options, ranging from never or less than once per month to six or more times per day. Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion according to food-composition tables from the U.S. Department of Agriculture (19) and other sources.

A full description of the SFFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity were reported previously (18). The correlation coefficient for energy-adjusted fiber intake between the SFFQs and diet records was 0.60. All nutrients, as well as the dietary fiber, were adjusted for total energy intake using regression analysis. This approach is based on the concept that the composition of the diet, independent of total energy intake, is most relevant to dietary recommendations (18).

Identification of Cases of Cholecystectomy

We inquired about occurrence and date of cholecystectomy on each biennial questionnaire starting in 1980. A validation study of the self report was conducted in a random sample of 50 nurses who reported a cholecystectomy in 1982. Forty-three out of 50 participants responded, and of these, all reiterated their earlier report, and surgery was confirmed in all 36 for whom medical records could be obtained. We chose cholecystectomy as an end point mainly because gallstone disease is mostly treated surgically (20), and because women are more likely to accurately report the occurrence and timing of a surgical procedure rather than untreated gallstones. In addition, symptomatic gallstones are the main indication for cholecystectomy.

Statistical Analysis

We calculated person-time of follow-up for each participant from the date of return of the 1984 questionnaire to the date of cholecystectomy, cancer, date of last questionnaire return, death, or the end of the study period in 2000, whichever came first. Women were categorized in quintiles of dietary fiber intake. Incidence rates were calculated by dividing the number of events by person-years of follow-up in each quintile. Relative risks were calculated as the incidence rate of cholecystectomy among women in different categories of exposures compared with the incidence rate among women in the reference category, with adjustment for age in 5-yr categories. The incidence of cholecystectomy was examined in relation to the cumulative average of exposure variables from all available questionnaires up to the start of each 2-yr follow-up interval, using methods for repeated measurement (21). Age-adjusted relative risks were calculated using the Mantel-Haenszel summary estimator (22). Multivariate relative risks were computed using the Cox proportional hazards regression model (23). In multivariate analyses, we simultaneously adjusted for the known or suspected confounding variables: time period, age, body mass index, weight change in the previous 2-yr interval, physical activity, parity, oral contraceptive use, postmenopausal hormone use, pack-years of smoking, thiazide diuretics, nonsteroidal antiinflammatory drugs, carbohydrate, protein, saturated fat, trans fat, alcohol, coffee, and total energy intake. Tests of linear trend across increasing quintiles of fiber intake were conducted by assigning the median value to each quintile and treating these as a single continuous variable. All relative risks are presented with 95% confidence intervals (CI), and all reported *p*-values are two-sided. All analyses were performed with Statistical Analysis System software, release 8.2 (SAS Institute, Cary, North Carolina).

RESULTS

At baseline in 1984, the mean dietary fiber intake varied approximately two-fold between the highest and lowest quintiles in the study population (Table 1). Women with a higher fiber intake consumed more carbohydrate, but had lower intakes of saturated fat, trans fat, and monounsaturated fat. Women who reported a high fiber intake tended to be more physically active, less likely to be current smokers, and to consume less alcohol and coffee. Pearson correlations among dietary fiber and major macronutrients showed that intake of total dietary fiber was positively correlated with carbohydrate intake (r = 0.43), was negatively correlated with total fat intake (r = −0.36), and was weakly correlated with protein intake (r = 0.14) (Table 2). The fiber fractions were correlated with each other to varying degrees. A strong correlation was observed between soluble and insoluble fibers (r = 0.77).

During 932,675 person-years of follow-up from 1984 to 2000, we ascertained 5,771 cases of cholecystectomy. After adjustment for age, the estimated relative risk for women in

Table 1. Baseline Characteristics of 69,778 U.S. Women with Cholecystectomy According to Quintiles of Energy-Adjusted Dietary Fiber in the Nurses' Health Study, 1984–2000

	Quintiles of Fiber Intake				
Characteristics	1 (Lowest)	2	3	4	5 (Highest)
Participants (n)	13, 983	13, 823	13, 817	14, 283	13, 872
Mean age (yr)	47.7	47.8	47.9	48.2	48.4
Current smoker (%)	35	25	20	17	13
Mean current body mass index (kg/m^2)	24.7	24.9	24.9	24.8	24.5
Physical activity (METs)*	6.7	7.2	7.4	8.0	8.6
Any weight loss in prior 2 yr (%)	26.2	25.7	26.4	27.2	30.0
Total energy (kcal/d)	1, 709	1, 756	1, 776	1, 768	1, 715
Mean parity (number of births)	2.9	3.0	2.9	2.9	2.8
History of oral contraceptive use (%)	51	50	50	49	47
Use of HRT (%)[†]	20	20	21	23	23
Use of aspirin (%)	29	27	28	28	31
Use of thiazide diuretics (%)	11	12	12	12	13
Protein (g/d)	69	70	71	73	74
Alcohol (g/d)	11.7	7.8	6.5	5.4	4.3
Coffee (cups)	2.1	1.9	1.8	1.7	1.5
Saturated fat (g/d)	24	23	22	21	19
Trans fat (g/d)	3.6	3.7	3.5	3.2	2.7
Polyunsaturated fat (g/d)	11	12	12	12	11
Monounsaturated fat (g/d)	24	24	23	22	19
Carbohydrate (g/d)	167	176	183	191	207
Dietary fiber (g/d)					
Total	10.6	13.6	15.7	18.3	23.7
Cereal	2.0	3.3	4.4	6.2	12.2
Vegetable	3.5	5.0	6.2	7.6	11.2
Wheat	1.4	2.2	2.9	3.9	7.0
Fruit	1.0	2.0	3.0	4.3	7.2
Cruciferous	0.3	0.5	0.8	1.2	2.3
Soluble	3.2	4.2	4.8	5.5	7.0
Insoluble	7.6	9.9	11.6	13.5	17.6

*Metabolic equivalent tasks per week, defined as a multiple of metabolic equivalent of sitting at rest.
[†]HRT = hormone replacement therapy. Only postmenopausal women were included.

the highest quintile compared with those in the lowest quintile of energy-adjusted dietary fiber intake was 0.94 (95% CI, 0.86–1.02, *p* for trend = 0.07) (Table 3). This association became significant after further adjustment for other suspected or known risk factors for gallstone. In an analysis that included age, body mass index, recent weight change, parity, oral contraceptive use, hormone replacement therapy, physical activity, pack-years of smoking, thiazide diuretics, nonsteroidal antiinflammatory drugs, total energy intake, glycemic load, saturated fat, trans fat, protein, alcohol, and coffee, the relative risk for the highest compared with the lowest quintile of dietary fiber intake was 0.87 (95% CI, 0.78–0.96, *p* for trend = 0.005). We also analyzed total dietary fiber as a continuous variable. From the multivariate analysis, each 5-g increment in total fiber intake corresponded to a relative risk of cholecystectomy of 0.94 (95% CI, 0.90–0.98).

The physiological consequences of a high-fiber diet may depend on the type of fiber. In the multivariate analyses separately, we found that the relative risk for women in the highest compared with lowest quintile of insoluble fiber intake was 0.83 (95% CI, 0.75–0.92, *p* for trend = 0.001). Other types

of dietary fiber were not significantly associated with risk of cholecystectomy.

Because the correlation between soluble and insoluble fibers was 0.77, in a multivariate analysis controlling for soluble and insoluble fiber types simultaneously, we found that the significant inverse association for insoluble fiber intake persisted. When extreme quintiles were compared, women in the highest quintile of insoluble fiber intake had a relative risk of 0.83 (95% CI, 0.73–0.94, *p* for trend = 0.009), and women in the highest quintile of soluble fiber intake had a relative risk of 1.01 (95% CI, 0.89–1.15, *p* for trend = 0.9). For a 5-g increase in insoluble fiber intake, the relative risk was 0.90 (95% CI, 0.84–0.97). For a 5-g increase in soluble fiber intake, the relative risk was 1.01 (95% CI, 0.83–1.23).

Because few foods contain only soluble or insoluble fiber, we also evaluated the effects of three main food sources of dietary fiber: cereal, vegetable, and fruit fibers. In a multivariate analysis, after simultaneously adjusting for each of the three main sources of fiber, women in the highest quintile of cereal fiber intake had a relative risk of 1.00 (95% CI, 0.90–1.10, *p* for trend = 0.7) compared with those in the lowest

Table 2. Energy-Adjusted Correlations among Different Types of Dietary Fiber, Intakes of Total Fat, Protein, and Carbohydrate at Baseline

Dietary Variables	Spearman Correlation Coefficients										
	1	2	3	4	5	6	7	8	9	10	11
Total dietary fiber (1)	1.00										
Cereal (2)	0.49	1.00									
Vegetable (3)[a]	0.66	0.08	1.00								
Wheat (4)	0.36	0.82	−0.01	1.00							
Fruit (5)[b]	0.68	0.18	0.31	0.08	1.00						
Cruciferous (6)	0.43	0.04	0.60	−0.04	0.24	1.00					
Soluble (7)	0.87	0.40	0.59	0.30	0.66	0.44	1.00				
Insoluble (8)	0.89	0.59	0.62	0.51	0.49	0.37	0.77	1.00			
Total fat (9)	−0.36	−0.26	−0.19	−0.14	−0.34	−0.14	−0.35	−0.30	1.00		
Protein (10)	0.14	−0.01	0.24	−0.07	0.11	0.23	0.07	0.11	0.12	1.00	
Carbohydrate (11)	0.43	0.38	0.12	0.30	0.39	0.04	0.46	0.40	−0.69	−0.40	1.00

[a]Vegetable was defined as a composite score of all the vegetable items, including cruciferous vegetables, dark yellow vegetables, tomatoes, green leafy vegetables, legumes, and other vegetables such as corn, mixed vegetables, celery, eggplant, mushroom, and beet.
[b]Fruit was defined as a composite score of all the fruit items in the questionnaire, including apple, pear, orange, grapefruit, peach, banana, strawberry, blueberry, cantaloupe, raisin, prune, and fruit juices.

quintile. When extreme quintiles were compared, women in the highest quintile of vegetable fiber intake had a relative risk of 0.95 (95% CI, 0.86–1.04, p for trend = 0.2), and women in the highest quintile of fruit fiber intake had a relative risk of 0.99 (95% CI, 0.89–1.09, p for trend = 0.7). Because relative risks between extreme quintiles from each fiber source are not directly on a gram-by-gram basis, we performed a separate multivariate analysis using fiber from each of the three

Table 3. Adjusted Relative Risks of Cholecystectomy According to Quintiles of Energy-Adjusted Dietary Fiber among U.S. Women in the Nurses' Health Study, 1984–2000

	Quintiles of Fiber Intake					
	(Lowest) 1	2	3	4	(Highest) 5	p for Trend
Total dietary fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.05 (0.96–1.14)	1.07 (0.99–1.17)	1.01 (0.93–1.10)	0.94 (0.86–1.02)	0.07
Multivariate[a] relative risk (95% CI[b])	1.00	0.95 (0.87–1.04)	0.94 (0.86–1.04)	0.89 (0.81–0.98)	0.87 (0.78–0.96)	0.005
Insoluble fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.03 (0.95–1.13)	1.08 (0.99–1.17)	1.07 (0.98–1.17)	0.91 (0.83–0.99)	0.07
Multivariate[a] relative risk (95% CI[b])	1.00	0.94 (0.86–1.02)	0.94 (0.86–1.03)	0.93 (0.85–1.03)	0.83 (0.75–0.92)	0.001
Soluble fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.07 (0.99–1.17)	1.10 (1.01–1.19)	1.06 (0.97–1.15)	1.01 (0.93–1.11)	0.89
Multivariate[a] relative risk (95% CI[b])	1.00	0.98 (0.90–1.07)	0.97 (0.89–1.06)	0.94 (0.86–1.03)	0.91 (0.83–1.01)	0.06
Cereal fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.08 (0.99–1.18)	1.19 (1.10–1.29)	1.17 (1.08–1.28)	1.03 (0.95–1.13)	0.69
Multivariate[a] relative risk (95% CI[b])	1.00	1.02 (0.94–1.17)	1.04 (0.96–1.13)	1.01 (0.92–1.10)	1.00 (0.91–1.10)	0.71
Cruciferous fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.00 (1.02–1.19)	0.94 (0.86–1.02)	1.01 (0.93–1.10)	0.98 (0.90–1.06)	0.81
Multivariate[a] relative risk (95% CI[b])	1.00	0.98 (0.90–1.07)	0.90 (0.82–0.98)	0.95 (0.87–1.04)	0.92 (0.84–1.01)	0.07
Fruit fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.08 (0.99–1.17)	1.10 (1.01–1.19)	1.04 (0.95–1.13)	1.00 (0.91–1.09)	0.66
Multivariate[a] relative risk (95% CI[b])	1.00	1.00 (0.92–1.09)	1.00 (0.91–1.09)	0.98 (0.89–1.07)	0.97 (0.88–1.08)	0.50
Vegetable fiber						
Age-adjusted relative risk (95% CI[b])	1.00	0.99 (0.91–1.08)	0.97 (0.89–1.05)	0.94 (0.87–1.02)	0.93 (0.85–1.01)	0.03
Multivariate[a] relative risk RR(95% CI[b])	1.00	0.95 (0.87–1.03)	0.95 (0.87–1.03)	0.90 (0.82–0.98)	0.95 (0.86–1.04)	0.20
Wheat fiber						
Age-adjusted relative risk (95% CI[b])	1.00	1.11 (1.02–1.21)	1.09 (1.00–1.18)	1.06 (0.98–1.15)	1.04 (0.96–1.13)	0.93
Multivariate[a] relative risk RR(95% CI[b])	1.00	1.04 (0.95–1.13)	0.99 (0.91–1.08)	0.97 (0.89–1.06)	0.99 (0.90–1.08)	0.45

[a]Multivariate model included the following: age (1-yr categories), time period (1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), body mass index at the beginning of each 2-yr 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, and ≥40), weight change in the previous 2 yr (≥10 pound weight loss, 5.0–9.9 pound weight loss, maintained weight ± 4.9 pounds, 5.0–9.9 pound weight gain, ≥10 pound weight gain), parity (0, 1, 2–3, ≥4 births), oral contraceptive use (ever, 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), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, ≥65), thiazide diuretics (yes or no), nonsteroidal antiinflammatory drugs (0, 1–6, ≥7 times per week, and dose unknown), intake of total energy (quintiles), energy-adjusted dietary glycemic load (quintiles), energy-adjusted protein (quintiles), energy-adjusted saturated fat (quintiles), energy-adjusted *trans* fats (quintiles), alcohol (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0 grams per day), and coffee (0, 1, 2–3, 4+ cups per day).
[b] CI = confidence interval.

Table 4. Multivariate Relative Risks of Cholecystectomy Stratified by Selective Risk Factors According to Dietary Fiber Intake among US Women in the Nurses' Health Study

	Total Fiber Intake					
Variables	1 (Lowest)	2	3	4	5 (Highest)	*p* for Trend
Age						
≤ 60 yr	1.0	0.98	0.99	0.94	0.86	0.03
> 60 yr	1.0	0.88	0.86	0.79	0.83	0.07
Body mass index (kg/m^2)						
≤ 25	1.0	1.00	0.99	0.93	0.86	0.01
> 25	1.0	0.93	0.97	0.90	0.95	0.50
Current smoking						
No	1.0	0.93	0.90	0.89	0.89	0.06
Yes	1.0	0.98	1.07	0.85	0.75	0.005
Physical activity [a]						
Low	1.0	0.91	0.95	0.85	0.96	0.40
High	1.0	0.99	0.95	0.91	0.81	0.001
Current alcohol use						
No	1.0	0.94	1.01	0.92	0.91	0.20
Yes	1.0	0.96	0.91	0.86	0.83	0.009
Coffee intake						
No	1.0	0.98	0.89	0.92	0.88	0.10
Yes	1.0	0.92	0.98	0.86	0.85	0.02

The multivariate model included the same covariates as in Table 3. The variable used for stratification was excluded from the model.
[a] Median values were used as the cut-off points.

sources as a continuous variable. When the main sources of fiber were controlled simultaneously, the relative risk of a 5-g increment of fiber from cereal was 0.99 (95% CI, 0.92–1.05), that from vegetable was 0.96 (95% CI, 0.89–1.03), and that from fruit was 0.98 (95% CI, 0.90–1.07).

To examine whether the association with total dietary fiber intake might be modified by other risk factors for gallstone disease, we repeated the multivariate analyses within subgroups of potential confounding variables (Table 4). The inverse associations between total dietary fiber intake and risk of cholecystectomy were seen in virtually all subgroups, although they were not always statistically significant.

To examine the possibility that latent gallstone symptoms caused a change in diet, thereby biasing the results, we conducted an analysis excluding all cases that occurred during the first 4-yr follow-up period. Compared with women in the lowest quintile of total dietary fiber intake, women in the highest quintile of total dietary fiber had a multivariate relative risk of 0.82 (95% CI, 0.73–0.92, *p* for trend = 0.0002).

DISCUSSION

In this large prospective cohort study, we found that diets high in fiber, especially insoluble fiber, significantly reduce risk of cholecystectomy. Women with a high fiber intake tended to have a generally healthy lifestyle (see Table 1), which may protect against gallstone disease. Our detailed analyses took into account the differences in lifestyle, and these adjustments appeared to strengthen the associations, which indicated that the associations were independent of these known risk factors.

Studies examining the relationship of dietary fiber with the occurrence of gallstone disease have been inconclusive. In the United States, a 10-yr follow-up of nearly 5,000 women participating in the National Health and Nutrition Examination Survey suggested that low intake of dietary fiber increased the risk of hospitalization for gallstone disease (24). Evidence from experimental studies suggests that dietary fiber may reduce both total and LDL cholesterol through increased bile acid excretion and decreased hepatic synthesis of cholesterol; it may also lower triglyceride levels and increase insulin sensitivity (8). In the Zutphen prospective study, fiber intake was found to be inversely associated with hyperinsulinemia and insulin resistance (25), and, therefore, may reduce the risk of gallstone formation (6, 7). However, one intervention study found that a diet high in fiber and low in refined carbohydrates did not reduce the risk of recurrence of gallstones after dissolution (26).

In most of the studies the effects of different types of dietary fiber were not addressed. Because the physiological influence of a high-fiber diet may depend on the type of fiber and the food source, we examined the effects of total dietary fiber as well as various types of fiber in our cohort. We found that insoluble fiber intake had a significant inverse association with risk of cholecystectomy. Insoluble fiber is typically the main component of dietary fiber intake, because nearly all fiber-containing foods have more insoluble than soluble dietary fiber. Approximately two-thirds to three-fourths of the dietary fiber in typical mixed-food diets is water insoluble (27). The effects of dietary fibers have been suggested to be related to their influence on bile acid metabolism (28, 29). Dietary insoluble fiber intake may speed intestinal transit, reduce the generation of secondary bile acids, and help

decrease cholesterol saturation in the bile (11, 12). However, the mechanisms that explain all the reduction of the risk may be largely unknown. Fiber from different food sources may differ in their bile acid binding capacity and glycemic response. Most experimental studies can only examine the metabolic effects of a diet high in insoluble fiber over several weeks; the long-term influence of a diet high in insoluble fiber on glucose control, plasma lipids, and insulin homeostasis is not yet established. Also, prolonged dietary fiber intake may be accompanied by structural alterations of the small intestine (30). Whether these intestinal changes are related to the changes in bile acid metabolism is not clear. Alternatively, we may not have sufficient independent variation in differentiating the inverse associations with risk of cholecystectomy between intakes of soluble and insoluble fibers.

In this cohort the possibility of misclassification might be of concern because information on nutrient intake was collected by self report. Random within-person variation could attenuate any true association of interest, but the SFFQ was designed to minimize this error by assessing average long-term dietary intake during the successive follow-up periods. These repeated measurements took into account possible changes in diet with time, and reduced random variation in reporting. Although the total effect of dietary fiber may not be fully captured by the questionnaire, any measurement errors would be expected to be unrelated to the endpoints because of the prospective design. Thus, any nondifferential misclassification would most likely bias the relative risks toward null and weaken, rather than strengthen, any true relationship.

To address the possibility of detection bias due to latent gallstone disease, we incorporated a lag period of 4 yr between dietary assessment at baseline and subsequent cholecystectomy. The significant inverse association persisted after the first 4 yr of follow-up were excluded.

In this study it was not possible to use screening ultrasonography for the presence of gallstones. Hence, we focused on gallstone disease resulting in cholecystectomy. It is likely that there was considerable underascertainment of gallstones because most gallstones are asymptomatic. Some undiagnosed gallstone cases might be present at baseline prior to the reporting of dietary information. It was unlikely that the presence of asymptomatic gallstones at baseline was associated with the reporting. Since relative risk estimation in follow-up studies would not be biased by uniform underascertainment (22), our results were unlikely biased due to asymptomatic gallstones. We attempted to estimate the incidence of newly symptomatic gallstone disease resulting in cholecystectomy, which is an entity of direct clinical and public health importance.

In conclusion, these results suggest an important beneficial effect that a higher, long-term intake of dietary fiber, particularly insoluble fiber, can reduce risk of cholecystectomy in women. Our findings support the notion that the public should consume adequate amounts of dietary fiber.

REFERENCES

1. Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. Gallstone disease. BMJ 2001;322:91–4.
2. National Center for Health Statistics. National Hospital Discharge Survey. Advance data from vital and health statistics. Hyattsville, MD, 2000.
3. 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.
4. 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.
5. Paigen B, Carey MC. Gallstones. In: King RA, Rotter JI, Motulsky AG, eds. The genetic basis of common diseases, 2nd Ed. London: Oxford, 2002:298–335.
6. Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. Hepatology 2000;31:299–303.
7. 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.
8. Hunninghake DB, Miller VT, LaRossa JC, et al. Hypocholesterolemic effects of a dietary fiber supplement. Am J Clin Nutr 1994;59:1050–4.
9. Hallfrisch J, Scholfield DJ, Behall KM. Diets containing soluble oat extracts improve glucose and insulin responses of moderately hypercholesterolemic men and women. Am J Clin Nutr 1995;61:379–84.
10. Smith U. Carbohydrates, fat, and insulin action. Am J Clin Nutr 1994;59S:686–9.
11. Marcus SN, Wheaton KW. Intestinal transit rate, deoxycholic acid and the cholesterol saturation of bile: Three interrelated factors. Gut 1986;27:550–8.
12. Marcus SN, Wheaton KW. Effects of a new, concentrated wheat fiber preparation on intestinal transit, deoxycholic acid metabolism and the compositon of bile. Gut 1986;27:893–900.
13. Vanberge-Henegouwen GP, Portincasa P, Van Erpecum KJ. Effect of lactulose and fiber-rich diets on bile in relation to gallstone disease: An update. Scand J Gastroenterol 1997;32:68–71.
14. Schwesinger WH, Kurtin WE, Page CP, et al. Soluble dietary fiber protects against cholesterol gallstone formation. Am J Surg 1999;177:307–10.

15. Judd PA. Dietary fiber and gallstones. In: Leeds AR, ed. Dietary fiber perspectives: Reviews and bibliography, Vol. 1. London: John Libbey, 1985:40–6.

16. Trautwein EA, Kunath-Rau A, Erbersdobler HF. Effect of different varieties of pectin and guar gum on plasma, hepatic and biliary lipids and cholesterol gallstone formation in hamsters fed on high-cholesterol diets. Br J Nutr 1998;79:463–71.

17. Ullrich IH, Albrink MJ. Lack of effect of dietary fiber on serum lipids, glucose, and insulin in healthy young men fed high starch diets. Am J Clin Nutr 1982;36:1–9.

18. Willett WC. Nutritional epidemiology, 2nd Ed. New York: Oxford University Press, 1998.

19. US Department of Agriculture. Composition of foods—raw, processed, and prepared, 1963–1991. Agricultural handbook series no. 8. Washington, DC: Department of Agriculture, US Government Printing Office, 1992.

20. Sleisenger MH, Fordtran JS, eds. Gastrointestinal and liver disease: Pathophysiology, diagnosis, management. Philadelphia: WB Saunders, 2002.

21. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: A comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.

22. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.

23. Cox DR. Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.

24. Sichieri R, Everhard JE, Roth H. A prospective study of hospitalization with gallstone disease among women: role of dietary factors, fasting period and dieting. Am J Pub Health 1991;81:880–4.

25. Feskens EJ, Loeber JG, Kromhout D. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly study. Am J Epidemiol 1994;140:350–60.

26. Hood KA, Gleeson D, Ruppin DC, et al. Gall stone recurrence and its prevention: The British/Belgian Gall Stone Study Group's post-dissolution trial. Gut 1993;34:1277–88.

27. Life Sciences Research Office, Federation of American Societies for Experimental Biology. Physiological effects and health consequences of dietary fiber. Bethesda, MD, 1987.

28. Heaton KW. The role of diet in the aetiology of cholelithiasis. Nutr Abstr Rev 1984;54:549–60.

29. Wechsler JG, Wenzel H, Swobodnik W, et al. Influence of increased fibre intake on biliary lipids. Scand J Gastroenterol 1987;22:185–91.

30. Zhang JX, Bergman F, Hallmans G, et al. The influence of barley fibre on bile composition, gallstone formation, serum cholesterol and intestinal morphology in hamsters. APMIS 1990;98:568–74.