Published in final edited form as:

J Epidemiol Community Health. 2014 June ; 68(6): 565–570. doi:10.1136/jech-2013-203503.

Cholelithiasis and the risk of liver cancer: results from cohort studies of 134,546 Chinese men and women

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Abstract

Background—Cholelithiasis and cholecystectomy have been proposed as risk factors for liver cancer, but findings have been inconsistent. We assessed this association using data from the Shanghai Women's and Men's Health Studies.

Methods—History of cholelithiasis and cholecystectomy were reported at baseline and follow-up interviews and liver cancer diagnoses were ascertained from the Shanghai Cancer Registry and Vital Statistics Unit. Adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were calculated after adjustment for potential confounders.

Results—A history of cholelithiasis and cholecystectomy was reported by 9.5% and 3.6% of participants at baseline, respectively. After a total of 859,882 person-years of follow-up for

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CONTRIBUTORS

YBX contributed to the conception and design of the study; YBX, HLL, and YTG acquired data; EV, CY, XOS and YBX performed the statistical analysis and the interpretation of results; EV wrote the first draft; All authors contributed to the critical review of the manuscript and approved the final manuscript; The corresponding author (YBX) had full access to all of the data and the final responsibility for the decision to submit for publication.

COMPETING INTERESTS: None declared.

women and 391,093 for men, incident liver cancer was detected in 160 women and 252 men. A positive association was observed between a history of cholelithiasis or cholecystectomy and liver cancer in men (aHR 1.46; 95% CI: 1.02, 2.07) and women (aHR 1.55; 95% CI: 1.06, 2.26). Similar results were observed for cholelithiasis only, but cholecystectomy did not reach statistical significance. There was no strong evidence for detection bias of liver cancer due to cholelithiasis or cholecystectomy.

Conclusion—Our study suggests that cholelithiasis and possibly cholecystectomy may increase the risk of liver cancer.

Keywords

Medical subject heading key words; China; cholecystectomy; cholelithiasis; cohort studies; gallstones; liver neoplasms

INTRODUCTION

Worldwide, liver cancer ranks as the fifth incident cancer among men and seventh among women. Owing to the high fatality rate, it is the second most common cause of cancer death among men and sixth among women [1]. The burden of liver cancer resides largely in China, accounting for more than 50% of both incident liver cancer cases and deaths worldwide [1]. Currently, there are no standard screening methods for liver cancer which indicates that primary prevention of liver cancer is a priority to decrease the incidence and mortality from this malignancy.

Cholelithiasis (i.e. gallstones) has been previously considered as a disease of the West due to its association with diet and obesity [2–4]. Symptomatic cholelithiasis is often treated by cholecystectomy [5], removal of the gallbladder, with varying rates of elective and non-elective cholecystectomies worldwide [6–8]. In developed countries, gallstone disease has been estimated to affect anywhere from 10% to 15% of adults and cost approximately \$6.2 billion annually in the United States [9]. Both cholelithiasis and cholecystectomy have been proposed as risk factors for liver cancer. Previous epidemiological studies have detected inconsistent associations between cholelithiasis, cholecystectomy and liver cancer and many have relied on data from registries, which reduces the ability to adjust for important confounders [10–21]. Inconsistent results could be related to a number of factors including differences in study design, exposure assessment or population, and lack of confounder adjustment. Therefore, we evaluated the association of cholelithiasis and cholecystectomy with the risk of liver cancer using data from the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS).

METHODS

Study population

The designs for both the SWHS and SMHS have been published in detail previously [22, 23]. From 1996 to 2000, 74,941 women aged 40 to 70 years old from seven urban communities in Shanghai were recruited for the SWHS with an overall participation rate of 92.7%. From 2002 to 2006, 61,483 men aged 40 to 74 years old with no previous cancer

were recruited for the SMHS from eight urban communities in Shanghai with an overall participation rate of 74.1%. Surveys and anthropometric measurements were collected by trained retired medical professionals. Follow-up interviews were conducted every two to three years for both the SWHS and SMHS. Informed consent was obtained from all participants and both cohorts were approved by all relevant Institutional Review Boards.

Exposure

History of cholelithiasis was assessed at baseline and in a subsequent follow-up questionnaire. At baseline, participants were asked if they had ever been diagnosed with cholelithiasis by a physician and if so, the age at diagnosis. In the third follow-up interview for the SWHS and first follow-up interview for the SMHS, participants were asked if they had ever been diagnosed with cholelithiasis or gallstones by a physician and whether the diagnosis was confirmed by ultrasound or X-ray examination. At baseline, 8,161 women (11.15%) and 4,614 men (7.52%) reported having a history of cholelithiasis. Of participants who reported a history of cholelithiasis at baseline, 6,047 women (74.10%) and 3,244 men (70.31%) reported at the follow-up interview to have a history of cholelithiasis. Of participants who consistently reported having a diagnosis of cholelithiasis ($N = 6,047$ for SWHS and $N = 3,244$ for SMHS), 5,863 women (96.96%) and 3,174 men (97.84%) reported that the diagnosis was confirmed by ultrasound or X-ray examination.

Due to the discrepancy in reporting of cholelithiasis, we assessed the effect of different self-reported cholelithiasis exposures: (1) baseline reported cholelithiasis; (2) baseline and follow-up reported cholelithiasis using repeated measures; and (3) concordant reporting of cholelithiasis at baseline and follow-up (i.e. yes/yes or no/no for history of cholelithiasis).

History of cholecystectomy was assessed at baseline and updated in follow-up questionnaires. At baseline, participants in the SWHS and SMHS were asked if they had ever had a cholecystectomy, and if so, at what age it occurred. In subsequent follow-up, the participants were only asked about new cholecystectomy procedures since baseline, so we were unable to assess the consistency of reporting. Participants were categorized as having a history of cholecystectomy if they reported a previous cholecystectomy at baseline.

We additionally categorized participants as having either a history of cholelithiasis or cholecystectomy at baseline. We calculated the time since cholelithiasis and cholecystectomy as the difference between the reported age at the time of diagnosis of cholelithiasis or the receipt of cholecystectomy and the age that the participant developed cancer or was censored due to death, loss to follow-up or end of study.

Outcome

Participants in the both the SWHS and the SMHS were followed up by annual record linkage with the population-based Shanghai Cancer Registry for incident cancer diagnoses and the Vital Statistics Unit of the Shanghai Center of Disease Prevention and Control for mortality. Incident cancer cases identified through linkage with the Shanghai Cancer Registry were verified through home visits. Medical charts were reviewed for verification and to document cancer diagnosis and treatment information. Incident liver cancer was defined as a primary tumor with an ICD-9 code of 155 (malignant neoplasm of liver and

intrahepatic bile ducts). Specific sites, primary neoplasms of the liver (ICD-9 155.0) and of the intrahepatic bile ducts (ICD-9 155.1), were also considered. TNM staging data was available for some incident liver cancer cases (53.6%). Follow-up data was available through December 31, 2010.

Potential confounding variables

Information about potential confounders was collected at baseline. Demographic variables included age, sex, education level, and family income. Body mass index (BMI) was calculated from the height and weight of each participant measured at baseline (kg/m^2). Behavioral characteristics included cigarette smoking, alcohol consumption, menopausal status (for women only) and amount of leisure time physical activity per day in metabolic equivalent hours per day (MET hours/day). Total energy intake was assessed in a baseline food frequency questionnaire. Participants also reported family history of liver cancer, history of diabetes and history of hepatitis or chronic liver disease. Since missing data was minimal, missing responses were included in the most common category.

Statistical analysis

Women diagnosed with cancer prior to baseline ($N = 1,598$) were excluded from analysis. We excluded participants from both studies who were lost to follow-up shortly after enrollment, diagnosed with cancers of unknown origin, or had missing data on baseline cholelithiasis or cholecystectomy ($N = 146$ for SMHS and $N = 134$ for SWHS). After exclusions, 61,337 men and 73,209 women were available for analysis.

Analyses were conducted separately for each cohort. We calculated age-adjusted descriptive statistics by baseline reported cholelithiasis and/or cholecystectomy and used the Cochran-Mantel Haenszel test for categorical variables and the test of differences in least-squared means for continuous variables except for physical activity which was tested using ranks in a general linear model due to non-normality. We determined age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident liver cancer by categories of cholelithiasis and cholecystectomy using the Cox proportional hazards regression model. Entry time was defined as the age which the participant started in the SMHS or SWHS and exit time was defined as the age when the participant developed incident liver cancer or was censored due to death, loss to follow up, or end of study on December 31, 2010. We also calculated adjusted HRs (aHRs) including potential confounders in the models. We used a random-effects model to pool the summary estimates for cholelithiasis and cholecystectomy for men and women when the Cochrane Q statistic had a p value less than 0.1 for the test of heterogeneity, otherwise, fixed-effects models were used. We evaluated the proportional hazards assumption by including an interaction between the cholelithiasis and cholecystectomy categories with the logarithm of time. The interaction was not statistically significant so we assumed that there were no violations of proportional hazards.

A number of additional analyses were conducted. We evaluated the associations by liver cancer type. We additionally tested the exclusion of participants with a history of hepatitis or chronic liver disease and participants with a history of diabetes. We assessed the number of liver cancer cases identified within a short interval (i.e. less than 5 years) since diagnosis of

cholelithiasis or cholecystectomy at baseline to evaluate potential detection bias introduced by treatment for cholelithiasis. As an estimate of potential early detection of liver cancer due to increased surveillance, we also assessed the association between baseline reported cholelithiasis and/or cholecystectomy with stage of liver cancer at diagnosis and with liver cancer mortality using the Pearson chi-square test among participants who developed liver cancer during follow-up. Statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and a two-sided *P* value of 0.05 was considered statistically significant.

RESULTS

At baseline, a history of cholelithiasis was reported by 11.1% of women and 7.5% of men while 4.3% of women and 2.7% of men reported a previous cholecystectomy. The age-adjusted descriptive statistics according to baseline history of cholelithiasis and cholecystectomy are presented in Table 1. Participants with a history of cholelithiasis or cholecystectomy differed from those without a history on some factors including age, education, smoking history and leisure time physical activity (Table 1).

After a total of 859,882 and 391,093 person-years of follow-up for women and men, respectively, incident liver cancer was detected in 160 women and 252 men. Among the liver cancer cases in women, 97 were primary liver, 45 were intrahepatic bile duct, and 18 were unspecified. In men, 155 cases were primary liver, 20 were intrahepatic bile duct and 97 were unspecified. Similar associations were observed between a history of either cholelithiasis or cholecystectomy and incident liver cancer both among women (HR 1.74; 95% CI: 1.20, 2.53) and men (HR 1.74; 95% CI: 1.22, 2.46) in age-adjusted analyses. After adjustment for confounders, the associations were attenuated, but remained statistically significant. When the multivariable adjusted estimates were pooled for men and women, the adjusted HR for incident liver cancer was 1.50 (95% CI: 1.16, 1.94) for participants with a history of cholelithiasis or cholecystectomy at baseline. A similar association estimate was observed for a history of cholelithiasis at baseline (pooled aHR 1.49; 95% CI: 1.15, 1.94) and the association estimate was strengthened for the model which updated the cholelithiasis exposure based on follow-up reporting (pooled aHR 1.74; 95% CI: 1.36, 2.22). The concordantly reported cholelithiasis pooled estimate was weaker than both the baseline only and updated exposure model (pooled aHR 1.39; 95% CI: 0.98, 1.96). Although a history of cholecystectomy increased the risks of liver cancer in both men and women, none of the observed associations reached statistical significance (Table 2).

When primary liver cancer (ICD-9 155.0) was the outcome, the results for women were generally similar to the overall analyses. For men, the associations with primary liver cancer were generally strengthened from the overall analyses. There were insufficient cases of intrahepatic bile duct cancer to conduct analyses (results not shown). When participants with a self-reported history of hepatitis or chronic liver disease were excluded from analysis, all observed associations for women were strengthened and were generally weakened for men. When participants with a self-reported history of diabetes were excluded, observed associations for both women and men were strengthened (results not shown).

Among participants with a self-reported history of cholelithiasis at baseline who developed liver cancer during follow-up, only 4 cases (5.5%) were identified within 5 years of diagnosis. Similarly, among participants with a self-reported history of cholecystectomy at baseline who developed liver cancer during follow-up, only 1 case (3.8%) was identified within 5 years of cholecystectomy. Baseline reported cholelithiasis and cholecystectomy were not associated with stage of diagnosis of liver cancer or liver cancer death among participants who developed liver cancer. A higher proportion of participants with cholelithiasis presented with Stage IV liver cancer (40.48% versus 29.05%), although the difference was not statistically significant (results not shown).

DISCUSSION

In this large cohort study, we found that having a history of either cholelithiasis or cholecystectomy increased the risk of liver cancer by about 55% for women and 46% for men. When individually considered, only the association between cholelithiasis and liver cancer reached statistical significance. Both baseline reported cholelithiasis and analyses restricted to participants who consistently reported their history of cholelithiasis at baseline and follow-up yielded similar estimates. The association for the concordant reporting of cholelithiasis with liver cancer did not reach statistical significance, however, this is likely to be related to sample size since after exclusions, only 296 cases of liver cancer remained, compared to 412 in the other analyses. When primary liver cancer was considered, results were generally similar for women, but strengthened for men.

A number of studies also found that cholelithiasis was a significant risk factor for liver cancer; however the prospective studies were mostly based on registry data and were therefore unable to adjust for potentially important confounders, such as alcohol consumption [10–16]. For example, in Denmark, a standardized incidence ratio (SIR) of 1.4 (95% CI: 1.2, 1.8) was found for the association between gallstone disease and liver cancer, but when stratified by cholecystectomy status, the association was only significant among patients who had not had a previous cholecystectomy (SIR 1.9; 95% CI: 1.3, 2.6) [12]. A recent case-control study in the United States found an increase in the odds of liver cancer by 2.35 (95% CI: 2.18, 2.54) or people with a history of gallstones [17] while a large network of case-control studies conducted in Italy and Switzerland found no statistically significant association with an OR of 1.17 (95% CI: 0.83, 1.65) [18].

The literature is similarly conflicting about whether previous cholecystectomy is a risk factor for liver cancer [15–17, 19–21]. For example, a cohort in Taiwan estimated a SIR of 3.29 (95% CI: 2.55, 4.18) for liver cancer when comparing the incidence for people with a cholecystectomy to the general population [19]. A prospective study conducted in the United Kingdom identified an association between cholecystectomy and liver cancer (incidence rate ratio (IRR) 1.45; 95% CI: 1.09, 1.90), but when cancers identified less than 2 years prior to the cholecystectomy were excluded, no association was observed (IRR 0.91; 95% CI: 0.64, 1.25) [21]. Since we had few participants with a previous cholecystectomy who developed liver cancer (15 women and 11 men), we may have been underpowered to detect a statistically significant association, although we did estimate a 38% increased risk of liver

cancer in pooled analyses. Similarly, many of these studies were based on registry data and confounder adjustment was limited or not done which could lead to residual confounding.

Chronic inflammation is a commonly proposed pathway for carcinogenesis for numerous cancer sites including the liver [24]. Responses to chronic inflammation, such as oxidative stress and liver regeneration, may be related to the development of liver cancer [25]. Gallbladder inflammation, increased mucin secretion and oxidative stress are all common features of gallstone formation which may in turn affect the liver [26]. Treatment with cholecystectomy may decrease these risk factors for carcinogenesis by removing the affected organ. However, in an animal study [27], cholecystectomy increased accumulation of fat in the liver which may lead to non-alcoholic fatty liver disease and inflammation of the liver [28]. Our study may suggest that chronic inflammation related to cholelithiasis increases the risk of liver cancer, however future research should address the mechanism through which cholelithiasis and cholecystectomy may be related to liver carcinogenesis.

Misclassification of cholelithiasis and cholecystectomy was possible due to the self-reported nature of the data. However, we assessed the consistency of report and additional diagnostic information obtained through subsequent questionnaires. The estimates from the baseline reported cholelithiasis were assumed to have some measurement error, but no missing data, while the concordant reported estimates should have less measurement error, but more missing data and therefore, less power to detect the association. The estimates were similar between analyses which suggests that misclassification of the exposure may have not strongly influenced our results. However, even if the exposures were misclassified, misclassification would likely be non-differential due to the prospective nature of the study which would bias the results toward the null and underestimate the strength of the association.

Detection bias may have also influenced our results. Participants diagnosed with cholelithiasis or received a cholecystectomy may have increased surveillance due to their condition, which could lead to incidental detection of liver cancer. Increased risks of cancer have been observed shortly after diabetes diagnoses, a likely result of detection bias related to diabetes treatment [29]. When we considered the interval of time since diagnosis with cholelithiasis or cholecystectomy, less than 6% of liver cancer cases were identified within 5 years of diagnosis. Similarly, if detection bias were present, participants with cholelithiasis or cholecystectomy would likely be diagnosed at earlier stages or have decreased mortality; however, we did not identify any differences in stage at diagnosis or liver cancer mortality by history of cholelithiasis or cholecystectomy. Given these findings, there is little evidence that the associations were due to detection bias.

Other limitations of this study include that data on chronic hepatitis and liver disease were only available by self-report, so underreporting due to asymptomatic chronic liver disease or fibrosis was likely. In the general population in Shanghai, the prevalence of current hepatitis B and C infection has been estimated to be about 5.5% and 0.4%, respectively with a previous hepatitis B infection detected in about 27.6% of the population [30]. We were also unable to ascertain whether cholelithiasis or cholecystectomy occurred prior to or after

hepatitis infection so future work should assess whether cholelithiasis is associated with liver cancer independent of hepatitis infection.

This study also has important strengths. The SWHS and SMHS are both rigorously designed cohort studies with high participation and retention rates. All of the covariates were assessed prior to the development of cancer which should decrease misclassification bias. Also, we had a relatively large number of incident liver cancer cases and long follow-up on which to base this analysis.

In conclusion, cholelithiasis and cholecystectomy may be risk factors for liver cancer. People diagnosed with cholelithiasis may need increased surveillance for liver cancer. Future research should focus on the potential mechanisms of liver carcinogenesis related to cholelithiasis and cholecystectomy.

Acknowledgments

We would like to thank the participants and the staff from the Shanghai Women's and Men's Health Studies for their contribution to this research.

FUNDING

This work was supported by funds from the State Key Project Specialized for Infectious Diseases of China [No. 2008ZX10002-015 and 2012ZX10002008-002 to YBX]; the United States National Institutes of Health [R37 CA070867 and R01 HL095931 to WZ, and R01 CA082729 to XOS]; the Fogarty International Clinical Research Scholars and Fellows Program at Vanderbilt University [R24 TW007988-5 to XOS]; and the Cancer Prevention and Control Training Program at the University of Alabama at Birmingham funded through the National Institutes of Health [5R25 CA047888 to EV]. The funding organizations had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript. The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in JECH and any other BMJ PGL products and sublicenses such use and exploit all subsidiary rights, as set out in our license (<http://group.bmj.com/products/journals/instructions-for-authors/licence-forms>).

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WHAT IS ALREADY KNOWN ON THIS SUBJECT?

Cholelithiasis and cholecystectomy have been previously studied as potential risk factors for liver cancer, but results have been inconsistent and many studies have not adjusted for potentially important confounders. Therefore, considering this association in a well-defined cohort is important to assess the potential risk.

WHAT THIS STUDY ADDS?

In this large, prospective study of men and women in Shanghai, China, a history of cholelithiasis statistically significantly increased the risk of liver cancer. The association between cholecystectomy and liver cancer was weaker and did not reach statistical significance. Increased surveillance of patients with cholelithiasis for liver cancer may be warranted although research is needed to confirm these findings.

Table 1

Baseline Characteristics of Study Participants by Baseline Report of Cholelithiasis and/or Cholecystectomy in the Shanghai Women's Health Study (1996–2010) and Shanghai Men's Health Study (2002–2010)

	Baseline reported cholelithiasis and/or cholecystectomy	No baseline report of cholelithiasis or cholecystectomy	p value
Women (SWHS)			
Number of subjects	8,330	64,879	
Cholelithiasis	97.97%	0.00%	
Cholecystectomy	37.83%	0.00%	
Age (years)	56.46 (0.10)	52.00 (0.04)	< 0.01
Educational level (%)			
Elementary school	19.74%	21.66%	< 0.01
Middle school	36.20%	37.29%	
High school	28.31%	27.84%	
College	15.75%	13.21%	
Annual family income (%)			
< 10,000 yuan	15.51%	16.18%	< 0.01
10,000 – 19,999 yuan	37.05%	38.39%	
20,000 – 29,999 yuan	28.78%	28.00%	
30,000 yuan	18.66%	17.43%	
Cigarette smoking (%)	3.46%	2.69%	< 0.01
Alcohol consumption (%)	2.25%	2.27%	0.51
Post-menopausal (%)	49.81%	48.76%	< 0.01
BMI (kg/m ²)	24.71 (0.04)	23.92 (0.01)	< 0.01
Leisure time physical activity (MET hours/day) Median (Q1, Q3)	0.00 (0.00, 1.37)	0.00 (0.00, 0.64)	< 0.01
Total energy intake (Kcal/day)	1646.36 (4.48)	1680.69 (1.59)	< 0.01
History of diabetes (%)	7.41%	3.83%	< 0.01
History of hepatitis/chronic liver disease (%)	5.65%	3.03%	< 0.01
Family history of liver cancer (%)	3.84%	3.22%	0.01
Men (SMHS)			
Number of subjects	4,785	56,552	
Cholelithiasis	96.43%	0.00%	
Cholecystectomy	35.19%	0.00%	
Age (years)	59.91 (0.14)	54.97 (0.04)	< 0.01
Educational level (%)			
Elementary school	5.43%	6.77%	< 0.01
Middle school	28.25%	33.45%	
High school	35.97%	37.00%	
College	30.35%	22.78%	
Annual per capita family income (%)			
< 6,000 yuan	10.17%	12.72%	< 0.01

	Baseline reported cholelithiasis and/or cholecystectomy	No baseline report of cholelithiasis or cholecystectomy	p value
6,000 – 11,999 yuan	38.73%	43.06%	
12,000 – 23,999 yuan	38.95%	34.70%	
24,000 yuan	12.14%	9.52%	
Cigarette smoking (%)	66.08%	69.94%	< 0.01
Alcohol consumption (%)	27.31%	34.21%	< 0.01
BMI (kg/m ²)	24.34 (0.04)	23.67 (0.01)	< 0.01
Leisure time physical activity (MET hours/day) Median (Q1, Q3)	0.00 (0.00, 1.99)	0.00 (0.00, 1.05)	0.55
Total energy intake (Kcal/day)	1890.81 (7.02)	1910.67 (2.03)	0.01
History of diabetes (%)	10.05%	5.90%	< 0.01
History of hepatitis/chronic liver disease (%)	9.99%	5.13%	< 0.01
Family history of liver cancer (%)	3.89%	3.57%	0.30

For all characteristics except age, means (standard error) and percentages were adjusted for age at baseline. All P values, other than age, were adjusted for age. The P values were calculated using the Cochran-Mantel Haenszel test for a general association for categorical variables and the test of difference in least-squared means for continuous variables except for physical activity which was tested using ranks in a general linear model due to non-normality.

BMI: Body mass index; MET: metabolic equivalents.

Hazard ratios (HRs) for Association Between Cholelithiasis and/or Cholecystectomy With Liver Cancer Risk in the Shanghai Women’s Health Study (1996–2010) and Shanghai Men’s Health Study (2002–2010)

Table 2

	Shanghai Women’s Health Study					Shanghai Men’s Health Study					Pooled multivariable model (men and women)	
	N	Age adjusted HR	95% CI	Multi-variable HR	95% CI	N	Age adjusted HR	95% CI	Multi-variable HR	95% CI	Multi-variable HR	95% CI
Baseline cholelithiasis and/or cholecystectomy (Yes/No)	Cases: 37/123 Non-cases: 8,293/64, 756	1.74	1.20, 2.53	1.55	1.06, 2.26	Cases: 38/214 Non-cases: 4,747/ 56,338	1.74	1.22, 2.46	1.46	1.02, 2.07	1.50	1.16, 1.94
Baseline cholelithiasis (Yes/No)	Cases: 35/125 Non-cases: 8,126/ 64,923	1.66	1.14, 2.43	1.47	1.00, 2.17	Cases: 38/214 Non-cases: 4,576/ 56,509	1.80	1.27, 2.56	1.51	1.06, 2.15	1.49	1.15, 1.94
Repeated measures of cholelithiasis (Yes/No)	Cases: 8,136/ 64,978 T1: 25/70 T2: 18/47 Non-cases: 9,355/ 56,732	1.98	1.39, 2.82	1.80	1.25, 2.57	Cases: 4,593/ 56,623 T1: 4,114/ 45,422 Non-cases: 4,114/ 45,422	1.94	1.39, 2.72	1.69	1.20, 2.37	1.74	1.36, 2.22
Concordant reported cholelithiasis (Yes/No) ^A	Cases: 15/62 Non-cases: 6,032/ 56,789	1.68	0.95, 2.97	1.49	0.83, 2.66	Cases: 24/195 Non-cases: 3,220/ 53,777	1.60	1.04, 2.46	1.34	0.87, 2.06	1.39	0.98, 1.96
Baseline cholecystectomy (Yes/No)	Cases: 15/145 Non-cases: 3,136/ 69,913	1.63	0.96, 2.79	1.56	0.91, 2.67	Cases: 11/241 Non-cases: 1,673/ 59,412	1.31	0.71, 2.40	1.18	0.64, 2.17	1.38	0.92, 2.07

N: Number; HR: Hazard ratio; CI: Confidence interval; T1: Baseline to follow-up interview; T2: Follow-up interview to the end of follow-up

Multivariable model adjusted for age, education, income, smoking status, alcohol consumption, menopausal status (for women only), family history of liver cancer, BMI, physical activity, total energy intake, and history of diabetes and hepatitis/chronic liver disease.

^AExcludes 10,311 women and 4,121 men who did not consistently report a history of cholelithiasis at baseline and follow-up (5,217 women and 2,603 men) or were missing follow-up data (5,094 women and 1,518 men).