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Family History of Gallstones and the Risk of Biliary Tract Cancer and Gallstones: A Population-based Study

Ann W. Hsing[1,*], **Yan Bai**[1], **Gabriella Andreotti**[1], **Asif Rashid**[2], **Jie Deng**[3], **Jinbo Chen**[1,4], **Alisa M. Goldstein**[1], **Tian-Quan Han**[5], **Ming-Chang Shen**[6], **Joseph F. Fraumeni Jr.**[1], and **Yu-Tang Gao**[3]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

[2]Department of Pathology, M.D. Anderson Cancer Center, Houston, TX, USA

[3]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

[4]Department of Epidemiology, University of Pennsylvania, Philadelphia, PA

[5]Department of Surgery, Ruijin Hospital, Second Medical University, Shanghai, China

[6]Zhongshan Hospital, Fudan University, Shanghai, China

Abstract

Background—Cancers of the biliary tract arise from the gallbladder, extrahepatic bile ducts, and ampulla of Vater. Although relatively uncommon, the incidence of biliary tract cancer rose more than 100% in Shanghai, China between 1972 and 1994. Gallstones are the predominant risk factor for biliary tract cancers, with over 60% of the cancer cases having gallstones. Familial tendency to gallstones has been reported and may further elevate the risk of gallbladder cancer. As part of a large population-based case-control study of biliary tract cancers in Shanghai, China, we examined the association between family history of gallstones and biliary tract cancers as well as biliary stones.

Methods—A total of 627 biliary tract cancers (368 gallbladder, 191 bile duct, 68 ampulla of Vater), 1,037 biliary stone cases (774 gallbladder, 263 bile duct), and 959 healthy subjects randomly selected from the population were included in this study. Information on family history of gallstones among first-degree relatives (i.e. parents, siblings, offspring) was obtained through a self-reported history during in-person interviews.

Results—A family history of gallstones was associated with increased risks of biliary stones (odds ratio (OR) =2.8, 95% confidence interval (CI) =2.1-3.8), gallbladder cancer (OR=2.1, 95% CI=1.4-3.3), and bile duct cancer (OR=1.5, 95% CI=0.9-2.5), after adjusting for age, gender, marital status, education, smoking, alcohol drinking, and body mass index. For gallbladder cancer, subjects with gallstones but without a family history of gallstones had a 21-fold risk (95% CI 14.8-30.1), while those with both gallstones and a positive family history had a 57-fold risk (95% CI 32.0-110.5). Significant risks for gallbladder cancer persisted after additional adjustment for gallstones, and when the analysis was restricted to subjects with first-degree relatives whose gallstones were treated with cholecystectomy. The significant associations with a family history of gallstones were seen for all first-degree relatives, including parents, siblings, and offspring, but not spouses.

[*]Correspondence to: Ann Hsing, Ph.D., Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, EPS 7058, MSC7234, 6120 Executive Blvd., Bethesda, MD 20852-7234, USA (hsinga@mail.nih.gov).

Conclusions—This large population-based study not only supports the role of gallstones in biliary carcinogenesis but also suggests that the underlying genetic or lifestyle determinants of stones within families contribute to the risk of biliary tract cancer.

Keywords

biliary tract cancer; cholelithiasis; familial aggregation; genetic susceptibility; China

Biliary tract cancers, encompassing tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater, are relatively uncommon malignancies in most parts of the world (1). The highest incidence rates have been observed among Native Americans and Hispanics living in the Southwestern United States and among some populations in Central and South America, Eastern Europe, and certain parts of Asia (1,2). Between 1972 to 1994, the incidence rates for biliary tract cancer rose more rapidly than those for any other malignancy in Shanghai, China, with increases of 119% among men and 124% among women (3). The increases in incidence were seen for all three biliary tract subsites in all age groups.

Gallstones are the most important risk factor for biliary tract cancers (1,4), especially for gallbladder cancer patients in whom 60-80% have a history of gallstones (1,5,6). Both gallstones and gallbladder cancer occur more frequently among women and older persons. Ethnic and familial predisposition suggests the role of genetic predisposition or shared lifestyle and metabolic factors, including obesity, insulin resistance, or high-fat, high-caloric diet (1, 7-9).

Familial aggregation of gallstones has been reported in several studies (10-12), but only one assessed the role of family history of gallstones in biliary tract cancer etiology. A case-control study of gallbladder cancer in Bolivia and Mexico reported that family history of gallstones was associated with a 3.6-fold risk of gallbladder cancer (13). The mechanisms are unclear, but it is possible that some yet unidentified susceptibility mechanism may further elevate the risk of biliary tract cancer associated with stones.

To investigate the rapid rise in incidence rates of biliary tract cancers in Shanghai, we conducted a large population-based study in Shanghai between 1997 and 2001. In this report, we examined whether a family history of gallstones is an independent risk factor for biliary tract cancer and whether it augments the risk associated with the presence of gallstones.

Materials and Methods

Study Subjects

Details of the study have been reported elsewhere (14-21). Briefly, cancer cases newly diagnosed with primary biliary tract cancer (ICD-9 156) between 1997 and 2000 were identified through a rapid-reporting system established by the Shanghai Cancer Institute (SCI) with 42 collaborating hospitals in urban Shanghai. This system captured more than 95% of all biliary tract cancers diagnosed in Shanghai. Case patients were permanent residents of urban Shanghai between 40 to 75 years of age. A total of 627 patients with biliary tract cancer (368 gallbladder, 191 bile duct, and 68 ampulla of Vater) were included. In addition, we selected a total of 1,037 biliary stone cases (774 gallbladder and 263 bile duct) from the same hospitals from which the cancer cases were selected. Biliary stone cases had no history of cancer and were matched to index cancer cases on gender, age (within 5 years), and hospital. A total of 959 healthy subjects who were randomly selected from the urban Shanghai population (6.5 million permanent residents), using the Shanghai Resident Registry records, were included in this study as population controls. Controls were free of non-skin cancer, and were frequency-matched to cancer cases in a 1-to-1 ratio by age (within 5 years) and gender distributions. All

study subjects provided written informed consent. The Institutional Review Boards of the National Cancer Institute and SCI approved the study protocol.

Clinical and Pathology Review

Confirmation of biliary tract cancer and biliary stone diagnoses involved the review of pathology slides, imaging data, medical records, and surgical reports. As part of the diagnostic procedures, all cancer cases underwent magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), or computed tomography (CT). Pathology slides were available for 70% of cancer cases who underwent surgery and were reviewed by a panel of pathologists. Imaging studies, pathology and surgical reports, and medical records were reviewed by a panel of clinicians, ultrasonographers, and pathologists for the presence of cancer. Biliary stone cases were confirmed by abdominal ultrasound and ERCP films, and by pathology review for those who underwent a cholecystectomy.

Interview

Study subjects who gave consent were interviewed by trained interviewers, using a structured questionnaire to obtain information on demographic, lifestyle, and dietary factors. Subjects were asked whether their first-degree blood relative(s), including parents, siblings, and offspring, as well as their spouse had ever been diagnosed with gallstones by a doctor. Study subjects were defined as having a family history of gallstones if at least one first-degree relative had a history of gallstones. If a positive family history of gallstones was reported, information on age at diagnosis and type of treatment, including cholecystectomy, was elicited. The response rate for interviews was over 95% among cases and 85% among controls. For quality-control purposes, all interviews were recorded and reviewed to ensure adherence to the study protocol. In addition, 5% of the subjects were randomly re-interviewed within three months of the first interview to assess reproducibility, and the concordance between the two interviews on responses to key questions was greater than 90%.

Gallstone Assessment

All study subjects were evaluated for the presence of gallstones. Among cancer cases, gallstone disease was identified by self-reported information from interview data and clinically from medical, surgical, and radiology records, including MRI, ERCP, CT, and ultrasound results. Among population controls, gallstone status was assessed by self-reported history and by abdominal ultrasound among those who gave consent for the procedure (85% of all population controls).

Statistical Analysis

Fisher's exact test was used to detect differences between cases and controls for selected characteristics. In order to make the appropriate case control comparisons, gallbladder cancer cases were compared with controls without a history of cholecystectomy; bile duct and ampulla of Vater cancer cases were compared with all controls; and biliary stone cases were compared with population controls without biliary stones. Those characteristics with statistically significant differences ($p<0.05$) were considered potential confounders for biliary tract cancers or stones.

To determine the risk of biliary tract cancers and stones associated with a family history of gallstones, we performed unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). In the full regression model, we adjusted for age, sex, education, smoking, alcohol consumption, body mass index (BMI; weight (Kg)/height (m^2)), and gallstones (for cancer cases); and in the parsimonious model, we adjusted for age and sex. To minimize misclassification of family history of gallstones, we also performed analysis

restricted to relatives who had had gallstones treated with cholecystectomy. Risk estimates were assessed by gender and gallstone status in order to determine whether either factor modified the risk of biliary tract cancers or stones associated with a family history of gallstones.

Results

Selected characteristics of the study subjects are shown in Table 1. As expected, most cases of gallbladder cancer (73.1%) and biliary stones (62.4%) were women, and only slightly more than half of bile duct (51.8%) and ampulla of Vater (54.4%) cancers were men. Compared with population controls, biliary stone cases were younger. Gallbladder cancer cases had fewer smokers, while bile duct and ampulla of Vater cancer cases had more smokers than controls. Gallbladder cancer and biliary stone cases had fewer subjects who drank alcohol but had higher BMI and more diabetes than controls. For all three cancer types, cases were significantly more likely to have had gallstones than controls. Median family size, including the number of siblings and children, was similar in cases and controls, although gallstone patients had a slightly smaller family size due to their slightly younger age.

A family history of gallstones was reported in 9.5% of population controls, 23.6% of biliary stone cases, and 19.3% of gallbladder cancer cases, 15.2% of bile duct cancer cases, and 14.7% of ampulla of Vater cancer cases (Table 1). Of subjects reporting a family history of gallstones, approximately 50% noted that their relatives had a history of cholecystectomy. Only 9 (0.3%) subjects (7 biliary stone cases and 2 bile duct cancer cases) reported a family history of biliary tract cancer; these numbers were too small to evaluate further.

A family history of gallstones was associated with excess risks of biliary stones (Table 2). After adjustment for age, gender, education, smoking status, alcohol drinking status and BMI, subjects with a family history of gallstones had a 2.8-fold risk of biliary stones (95% CI=2.1-3.8), compared with subjects without a family history. This estimate remained statistically significant when the analysis was restricted to subjects who had relatives with a history of biliary stones treated with cholecystectomy (OR=3.3, 95% CI 2.0-5.6). Those with more than one relative reporting a history of gallstones had a 2.3-fold risk of biliary stones (95% CI 1.7-3.1). Although gallstones were more common in women, the risk of stones associated with a positive family history did not differ substantially by gender of subjects or family members. A family history of gallstones was associated with excess biliary stone risk in all types of first degree relatives, with the highest risk seen for subjects having an affected sibling (OR=4.0, 95% CI 2.5-6.4), especially brothers (OR=5.0, 95% CI 2.3-10.8). No excess risk was associated with having a spouse with gallstones. The excess risk of gallstones associated with a family history of gallstones was more pronounced among diabetics (OR=5.5, 95% CI 1.6-19.2), although there was no significant interaction between diabetes and a family history of gallstones.

A family history of gallstones was also associated with a significantly increased risk of biliary tract cancer (Table 2). After adjustment for age, gender, BMI, and gallstones, subjects with a family history of gallstones had a risk of 2.1-fold for gallbladder cancer (95% CI 1.4-3.3), 1.5-fold for bile duct cancer (95% CI 0.9-2.5), and 1.5-fold for ampulla of Vater cancer (95% CI 0.7-3.2). When the analysis was restricted to subjects whose relatives had gallstones treated with cholecystectomy, the excess risks persisted for all subsites of biliary cancer and for subjects with two or more family members having gallstones, but was statistically significant only for gallbladder cancer (OR=1.4, 95% CI=1.0-1.8). The effect of a family history of gallstones on gallbladder cancer risk was more pronounced for women (OR=2.9, 95% CI= 1.9-4.5) than men (OR=1.8, 95% CI=0.9-3.4), although there was no significant interaction between gender and family history of gallstones (P for interaction = 0.23). We did not observe a difference in risk estimates between men and women for bile duct cancer, and there were too

few ampulla of Vater cancer cases to evaluate risk by gender. Regardless of the type of relative, family history of gallstones was associated with higher risks of biliary tract cancers. For gallbladder cancer the risk was highest for subjects having an offspring with stones (OR=2.9, 95% CI 1.4-6.2), particularly for those having an affected son (OR=4.0, 95% CI 1.0-15.7). A history of gallstones among spouses was associated only with a higher risk of bile duct cancer among male subjects (OR=3.3, 95% CI 1.4-7.5).

Table 3 shows the combined effect of having gallstones and a positive family history of gallstones on biliary tract cancer risk. Compared with subjects without either gallstones or a reported family history, those with gallstones but no family history had a 21-fold risk of gallbladder cancer (95% CI 14.8-30.1), while those with both gallstones and a family history had a 57-fold risk (95% CI 30.2-110.5). Regardless of BMI, diabetes, or hypertension, a family history of gallstones was associated with an increased risk of gallbladder cancer (data not shown). Similar risk patterns were seen for cancers of the bile duct and ampulla of Vater, with the highest risk among those with both stones and a positive family history.

Discussion

In this population-based study in Shanghai, China, a family history of gallstones was associated with a 2.8-fold risk of biliary stones and a 2-fold risk of biliary tract cancer, regardless of the number and type of first-degree relatives having gallstones. For gallbladder cancer, subjects with gallstones alone had a 21-fold risk, while those with both gallstones and a positive family history had a 57-fold risk. No association was found for gallstones among spouses.

The excess risk of biliary stones associated with a family history of gallstones is consistent with several previous studies in various population groups (22-25). Reasons for the much higher risk (4- to 5-fold) seen for subjects with a sibling or child having gallstones are unclear, but may be partly related to difficulty in recalling parents' gallstone histories or to detection bias among siblings. Although gallstones are more common in women than in men, the risk of gallstones related to a positive family history did not vary by gender, with a similar magnitude of risk regardless of whether the gallstones occurred in male or female relatives.

The 2-fold risk of biliary tract cancer associated with familial occurrence of gallstones was independent of gallstone status among subjects, and is consistent with risks reported in previous studies from various population groups, including the U.S., Japan, Mexico and Bolivia (13, 26), providing further support for the role of genetic susceptibility to both gallstones and biliary tract cancer. Although the risk of biliary tract cancer associated with a personal history of gallstones was in our study, with odds ratios of 25, 8, and 5 for cancers of the gallbladder, bile duct, and ampulla of Vater, respectively, the risk of biliary tract cancer associated with a family history of gallstones persisted after adjustment for gallstone status among study subjects. Although females are more likely to develop gallbladder cancer as well as stones; our study indicated that gender did not modify the association between a family history of gallstones and biliary tract cancer.

The very high risk (57-fold) of gallbladder cancer associated with both a personal history and a family history of gallstones suggests an interactive effect, although it was not statistically significant (p for interaction=0.18). This effect was not observed for cancers of the bile duct and ampulla of Vater, perhaps related to the smaller sample sizes or the lower risks associated with stones for these subsites of cancer. In our study, it was difficult to evaluate the risk of gallbladder cancer in relation to family history of gallstones in the absence of gallstones among study subjects, since nearly 84% of the cancer cases had gallstones and only 2.2% of the cases with a family history of gallstones did not have gallstones.

The underlying mechanism for the familial tendency to gallstone disease may be due to genetic susceptibility or shared lifestyle or metabolic factors. Although the association appeared independent of risk factors for gallstones, such as obesity and diabetes, it is difficult to tease apart genetic and lifestyle factors, given the likelihood of gene-environment interaction. For example, lipid levels in serum and bile affect the risk of gallstones, and are influenced by variants of genes in the lipid metabolism pathway (27-30) as well as lifestyle factors, such as obesity and diet (31). In addition, preliminary studies suggest susceptibility genes in the lipid metabolism pathway, including the *LDLR* and *APOE* genes (26,32,33). The role of genetic susceptibility is supported by our finding that biliary stones were not associated with gallstone history in spouses, although we cannot rule out the potential effect of early-life exposures. Further work is needed to identify the genetic and other mechanisms responsible for the lithogenic bile reported in high risk populations such as native Americans.

Similarly, it is unclear why a family history of gallstones further increases the risk of gallbladder cancer in our study. In addition to gallstones, the risk factors for gallbladder cancer tend to run in families, such as obesity, insulin resistance, high-fat or high-caloric diet, and altered lipid metabolism (6,9,10,13,33). We were unable to tease apart these factors, since gallstones and gallbladder cancer share similar risk factors, and we did not have lifestyle information from family members.

A number of strengths and limitations of the study should be noted. Given the high case ascertainment (>95%) and response rates (>85%), selection and survival biases were minimal. Also, the rigorous pathology and clinical confirmation of biliary tract cancer and stone diagnoses among cases minimized misclassification of outcome. This is one of the few studies of biliary tract cancer to have complete assessment of gallstone status among cancer cases and controls, which permitted an assessment of the family history of gallstones while controlling for subjects' gallstone status. Since the family history of gallstones was based on self-reported data and was not confirmed by medical records, some misclassification of family history of gallstones was possible. However, when the analysis was limited to relatives who had a cholecystectomy, the association between family history of gallstones and biliary tract cancer persisted. History of cholecystectomy is likely to underestimate the true prevalence of gallstones in family members in both cases and controls, since patients with gallstones are not necessarily treated with surgery. It is possible that given the strong association between gallstones and gallbladder cancer, relatives of cancer cases might be more knowledgeable or concerned about gallstone status, thereby increasing the likelihood of stone detection in family members. However, this bias should be minimal, since the diagnosis of gallstones in family members occurred prior to the diagnosis of cancer in study subjects, although some degree of recall bias among cases is possible. Underreporting of gallstones in family members due to asymptomatic gallstones is possible but is likely to be small, since only 6% of the controls who underwent abdominal ultrasound had silent gallstones. In addition, this misclassification is unlikely to be differential in cases and controls. Due to small numbers, we had limited statistical power to evaluate bile duct and ampulla of Vater cancers, or to test for interactions between family histories and other conditions.

In summary, data from this population-based study of biliary tract cancer indicate that a family history of gallstones among first-degree blood relatives augment the substantial risk associated with a personal history of stones as well as biliary tract cancer risk. These results suggest that genetic factors or shared environment may increase the familial tendency to gallstones and biliary tract cancer. The clustering of both conditions in families and populations provides an opportunity for epidemiologic studies incorporating genomic and metabolic approaches to clarify the genetic and other pathways involved in the development of biliary stones and cancer.

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Table 1

Selected characteristics of study subjects by case-control status

Selected Characteristics	Control Subjects			Biliary Stones	Biliary Tract Cancer		
	All[1]	Without cholecystectomy[2]	Without stones[3]	All stones[4]	Gallbladder	Bile Duct	Ampulla of Vater
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All subjects	959 (100.0)	902 (100.0)	735 (100.0)	1037 (100.0)	368 (100.0)	191 (100.0)	68 (100.0)
Gender							
Male	373 (38.9)	357 (39.6)	313 (42.6)	390 (37.6)*	99 (26.9)***	99 (51.8)***	37 (54.4)**
Female	586 (61.1)	545 (60.4)	422 (57.4)	647 (62.4)	269 (73.1)	92 (48.2)	31 (45.6)
Age at interview							
34-54	128 (13.3)	126 (14.0)	115 (15.6)	307 (29.6)***	49 (13.3)	30 (15.7)	6 (8.8)
55-64	269 (28.1)	259 (28.7)	207 (28.2)	298 (28.7)	96 (26.1)	47 (24.6)	20 (29.4)
65-75	562 (58.6)	517 (57.3)	413 (56.2)	432 (41.7)	223 (60.6)	114 (59.7)	42 (61.8)
Education							
Elementary	396 (41.3)	365 (40.5)	285 (38.8)	317 (30.6)**	198 (53.8)***	86 (45.0)	29 (42.6)
High school	423 (44.1)	405 (44.9)	336 (45.7)	537 (51.8)	129 (35.1)	74 (38.7)	31 (45.6)
Above high school	140 (14.6)	132 (14.6)	114 (15.5)	183 (17.6)	41 (11.1)	31 (16.2)	8 (11.8)
Marital status							
Married	751 (78.3)	703 (78.0)	584 (79.5)	884 (85.2)**	284 (77.2)	161 (84.3)	55 (80.9)
Divorced, widowed	196 (20.4)	187 (20.7)	143 (19.4)	143 (13.8)	81 (22.0)	28 (14.7)	13 (19.1)
Single	12 (1.3)	12 (1.3)	8 (1.1)	10 (1.0)	3 (0.8)	2 (1.0)	0 (0.0)
Ever smoked cigarettes [5]							
No	674 (70.3)	633 (70.2)	508 (69.1)	754 (72.7)	278 (75.8)	115 (60.2)	38 (55.9)
Yes	285 (29.7)	269 (29.8)	227 (30.9)	283 (27.3)	89 (24.2)*	76 (39.8)*	30 (44.1)*
Ever drank alcohol							
No	760 (79.2)	715 (79.4)	568 (77.4)	869 (83.9)***	316 (85.9)**	141 (73.8)	53 (77.9)
Yes	198 (20.6)	186 (20.6)	166 (22.6)	167 (16.1)	52 (14.1)	50 (26.2)	15 (22.1)
Body mass index (kg/m2)							
<18.5	84 (8.7)	83 (9.2)	70 (9.5)	51 (4.9)***	20 (5.4)***	11 (5.8)	1 (1.5)

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Selected Characteristics	Control Subjects			Biliary Stones	Biliary Tract Cancer		
	All[1]	Without cholecystectomy[2]	Without stones[3]	All stones[4]	Gallbladder	Bile Duct	Ampulla of Vater
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
18.5-22.9	400 (41.7)	386 (42.8)	336 (45.7)	345 (33.3)	130 (35.3)	85 (44.5)	29 (42.6)
23.0-24.9	198 (20.6)	185 (20.5)	147 (20.0)	263 (25.4)	73 (19.8)	49 (25.7)	15 (22.1)
≥25	277 (28.9)	248 (27.5)	182 (24.8)	378 (36.5)	145 (39.4)	46 (24.1)	23 (33.8)
Diabetes							
No	881 (91.9)	834 (92.5)	688 (93.6)	925 (89.3)***	316 (86.1)***	171 (89.5)	63 (92.6)
Yes	78 (8.1)	68 (7.5)	47 (6.4)	111 (10.7)	51 (13.9)	20 (10.5)	5 (7.4)
Hypertension							
No	553 (57.7)	526 (58.3)	441 (60.0)	695 (67.0)**	230 (62.5)	130 (68.1)**	48 (70.6)*
Yes	406 (42.3)	376 (41.7)	294 (40.0)	342 (33.0)	138 (37.5)	61 (31.9)	20 (29.4)
Gallstones							
No	735 (76.6)	735 (81.5)	735 (100.0)	0 (0.0)	60 (16.3)***	64 (33.5)***	32 (47.1)***
Yes	224 (23.4)	167 (18.5)	0 (0.0)	1037 (100.0)	308 (83.7)	127 (66.5)	36 (52.9)
Family history of gallstones [6]							
No	868 (90.5)	820 (90.9)	667 (90.7)	792 (76.4)***	297 (80.7)***	162 (84.8)*	58 (85.3)
Yes	91 (9.5)	82 (9.1)	68 (9.3)	245 (23.6)	71 (19.3)	29 (15.2)	10 (14.7)
Treated with cholecystectomy	49 (5.1)	43 (4.8)	33 (4.8)	0 (0.0)	36 (9.8)	11 (5.8)	6 (8.8)
Family history of any cancer [6]							
No	620 (65.9)	583 (65.7)	486 (66.9)	696 (68.2)	266 (74.7)**	120 (63.8)	42 (61.8)
Yes	321 (34.1)	304 (34.3)	240 (33.1)	325 (31.8)	90 (25.3)	68 (36.2)	26 (38.2)
Family history of biliary tract cancer [6]							
No	959 (100.0)	902 (100.0)	735 (100.0)	1030 (99.3)**	368 (100.0)	189 (99.0)	68 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
Have at least one sibling							
No	48 (5.0)	46 (5.1)	34 (4.7)	56 (5.4)	26 (7.1)	12 (6.3)	5 (7.5)
Yes	905 (95.0)	851 (94.9)	697 (95.3)	973 (94.6)	340 (92.9)	177 (93.7)	62 (92.5)
Have at least one offspring							
No	39 (4.1)	37 (4.1)	29 (4.0)	47 (4.5)	10 (2.7)	10 (5.3)	2 (2.9)

Selected Characteristics	Control Subjects			Biliary Stones	Biliary Tract Cancer		
	All[1]	Without cholecystectomy[2]	Without stones[3]	All stones[4]	Gallbladder	Bile Duct	Ampulla of Vater
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	918 (95.9)	863 (95.9)	704 (96.0)	988 (95.5)	358 (97.3)	180 (94.7)	66 (97.1)
Number siblings and offspring							
< 5	212 (22.1)	208 (23.1)	179 (24.4)	301 (29.0)*	78 (21.2)	43 (22.5)	10 (14.7)
5-7	398 (41.5)	374 (41.5)	297 (40.4)	427 (41.2)	146 (39.7)	83 (43.5)	30 (44.1)
8-9	193 (20.1)	182 (20.2)	148 (20.1)	186 (17.9)	83 (22.6)	38 (19.9)	18 (26.5)
≥ 10	156 (16.3)	138 (15.3)	111 (15.1)	123 (11.9)	61 (16.6)	27 (14.1)	10 (14.7)

[1] All population controls compared with bile duct and ampulla vater cancer cases

[2] Population controls who did not have a cholesectomy compared with gallbadder cancer cases

[3] Population controls without biliary stones compared to biliary stone cases

[4] Includes gallstones and bile duct stones

[5] Ever smoked cigarettes for at least 6 consecutive months

[6] At least one affected first-degree relative, i.e. parent, sibling, offspring

* p<0.05,

** p<0.01,

*** p<0.001 for Fisher's exact test for difference between cases and controls

Table 2

Odds ratios (ORs) and 95% confidence intervals (95% CI) for biliary tract stones and cancers in relation to family history of gallstones

Characterisitcs of a Family History of Gallstones	Control Subjects			Biliary Stones		Biliary Tract Cancer					
	All[1]	Without Cholecys-tectomy[2]	Without stones[3]	All Stones[4]		Gallbladder		Bile Duct		Ampulla of Vater	
	n (%)	n (%)	n (%)	n (%)	OR[5] (95% CI[5])	n (%)	OR[6] (95% CI[6])	n (%)	OR[6] (95% CI[6])	n (%)	OR[6] (95% CI[6])
All subjects	959 (100.0)	902 (100.0)	735 (100.0)	1037 (100.0)	- -	368 (100.0)	- -	191 (100.0)	- -	68 (100.0)	- -
Family history of gallstones[7]											
No	868 (90.5)	820 (90.9)	667 (90.7)	792 (76.4)	1.0 -	297 (80.7)	1.0 -	162 (84.8)	1.0 -	58 (85.3)	1.0 -
Yes											
Reported family history of gallstones	91 (9.5)	82 (9.1)	68 (9.3)	245 (23.6)	2.8 (2.1 - 3.8)	71 (19.3)	2.1 (1.4 - 3.3)	29 (15.2)	1.5 (0.9 - 2.5)	10 (14.7)	1.5 (0.7 - 3.2)
Family history of cholecystectomy	49 (5.1)	43 (4.8)	4 (0.5)	64 (6.2)	3.3 (2.0 - 5.6)	36 (9.8)	1.4 (1.0 - 1.8)	11 (5.8)	0.9 (0.7 - 1.4)	6 (8.8)	1.3 (0.8 - 2.0)
1 relative with a history of gallstones	84 (8.8)	77 (8.5)	33 (4.5)	118 (11.4)	1.7 (1.4 - 2.1)	62 (16.8)	2.1 (1.3 - 3.3)	24 (12.6)	1.4 (0.8 - 2.4)	7 (10.3)	1.2 (0.5 - 2.8)
> 1 relative with a history of gallstones	7 (0.7)	5 (0.6)	64 (8.7)	181 (17.5)	2.3 (1.7 - 3.1)	9 (2.4)	1.7 (0.8 - 3.3)	5 (2.6)	1.5 (0.8 - 2.9)	3 (4.4)	2.5 (1.2 - 5.3)
Male relative with a history of gallstones	25 (2.6)	23 (2.5)	20 (2.7)	86 (8.3)	3.3 (1.9 - 5.5)	22 (6.0)	2.4 (1.1 - 5.3)	11 (5.8)	2.4 (1.1 - 5.6)	3 (4.4)	1.8 (0.5 - 6.8)
Female relative with a history of gallstones	70 (7.3)	62 (6.9)	50 (6.8)	189 (18.2)	3.0 (2.1 - 4.2)	51 (13.9)	1.9 (1.2 - 3.2)	20 (10.5)	1.2 (0.7 - 2.2)	8 (11.8)	1.6 (0.7 - 3.6)
Parent with a history of gallstones	33 (3.4)	31 (3.4)	29 (3.9)	97 (9.4)	2.1 (1.3 - 3.3)	18 (4.9)	2.2 (1.0 - 4.8)	11 (5.8)	1.7 (0.8 - 3.8)	1 (1.5)	- -
Father	8 (0.8)	7 (0.8)	6 (0.8)	18 (1.7)	1.5 (0.6 - 3.9)	3 (0.8)	2.3 (0.5 - 11.8)	5 (2.6)	2.6 (0.7 - 9.4)	0 (0.0)	- -
Mother	25 (2.6)	24 (2.7)	23 (3.1)	82 (7.9)	2.3 (1.4 - 3.8)	15 (4.1)	2.2 (0.9 - 5.2)	7 (3.7)	1.5 (0.6 - 3.9)	1 (1.5)	- -
Sibling with a history of gallstones[8]	37 (4.1)	33 (3.9)	24 (3.4)	128 (13.2)	4.0 (2.5 - 6.4)	26 (7.6)	1.6 (0.8 - 3.1)	17 (9.6)	1.9 (0.9 - 3.7)	8 (12.9)	2.8 (1.2 - 6.8)
Brother[9]	10 (1.3)	10 (1.3)	8 (1.3)	51 (5.9)	5.0 (2.3 - 10.8)	9 (3.0)	1.6 (0.5 - 5.2)	5 (3.1)	3.0 (0.9 - 9.9)	3 (5.5)	4.3 (1.1 - 17.4)
Sister[10]	28 (3.6)	24 (3.3)	16 (2.7)	87 (10.4)	3.9 (2.2 - 6.9)	17 (6.0)	1.4 (0.6 - 3.2)	13 (8.3)	1.6 (0.7 - 3.3)	6 (10.9)	2.6 (0.9 - 7.0)
Offspring with a history of gallstones[11]	24 (2.6)	20 (2.3)	17 (2.4)	56 (5.7)	3.6 (2.0 - 6.3)	31 (8.7)	2.9 (1.4 - 6.2)	4 (2.2)	0.9 (0.3 - 2.8)	1 (1.5)	- -
Son[12]	7 (0.9)	6 (0.8)	6 (1.0)	22 (2.9)	3.5 (1.4 - 8.8)	10 (3.2)	4.0 (1.0 - 15.7)	1 (0.7)	- -	0 (0.0)	- -
Daughter[13]	18 (2.5)	15 (2.2)	12 (2.2)	38 (5.2)	3.6 (1.9 - 7.2)	21 (7.0)	2.4 (1.0 - 5.8)	3 (2.0)	0.8 (0.2 - 2.9)	1 (1.8)	- -
Reported spouse with history of gallstones[8]											
No	814 (86.0)	768 (86.3)	624 (85.8)	750 (73.0)	1.0 -	284 (77.8)	1.0 -	146 (77.2)	1.0 -	58 (85.3)	1.0 -
Yes	51 (5.4)	49 (5.5)	43 (5.9)	47 (4.6)	1.0 (0.6 - 1.6)	15 (4.1)	1.0 (0.5 - 2.1)	16 (8.5)	2.0 (1.0 - 3.8)	1 (1.5)	- -
Among male subjects	23 (6.3)	21 (6.0)	20 (6.5)	30 (7.8)	1.6 (0.9 - 2.9)	7 (7.1)	1.7 (0.5 - 5.4)	13 (13.4)	3.3 (1.4 - 7.5)	1 (2.7)	- -

Characterisitcs of a Family History of Gallstones	Control Subjects			Biliary Stones		Biliary Tract Cancer					
	All[1]	Without Cholecys-tectomy[2]	Without stones[3]	All Stones[4]		Gallbladder		Bile Duct		Ampulla of Vater	
	n (%)	n (%)	n (%)	n (%)	OR[5] (95% CI[5])	n (%)	OR[6] (95% CI[6])	n (%)	OR[6] (95% CI[6])	n (%)	OR[6] (95% CI[6])
Among female subjects	28 (4.8)	28 (5.2)	23 (5.5)	17 (2.6)	0.6 (0.3 - 1.1)	8 (3.0)	0.7 (0.3 - 1.9)	3 (3.3)	0.8 (0.2 - 2.9)	0 (0.0)	- -

[1] All population controls compared with bile duct and ampulla vater cancer cases

[2] Population controls without cholesectomy compared with gallbadder cancer cases

[3] Population controls without biliary stones compared to biliary stone cases

[4] Includes gallstone and bile duct stone cases

[5] Adjusted for age, gender, education, smoking, alcohol drinking, and BMI

[6] Adjusted for age, gender and gallstones

[7] At least one affected first-degree relative, i.e. parent, sibling, offspring

[8] Among subjects with at least one sibling

[9] Among subjects with at least one brother

[10] Among subjects with at least one sister

[11] Among subjects with at least one offspring

[12] Among subjects with at least one son

[13] Among subjects with at least one daughter

Table 3

Odds ratios (ORs) and 95% confidence Intervals (95% CI) for biliary tract cancers in relation to family history of gallstones and gallstone status

Family History of gallstones and gallstone status among subjects	Control Subjects		Biliary Tract Cancer					
	All[1]	Without Cholecystectomy[2]	Gallbladder Cancer		Bile Duct Cancer		Ampulla of Vater Cancer	
	n (%)	n (%)	n (%)	OR[3] (95% CI[3])	n (%)	OR[3] (95% CI[3])	n (%)	OR[3] (95% CI[3])
Total	959 (100.0)	902 (100.0)	368 (100.0)	- -	191 (100.0)	- -	68 (100.0)	- -
Family History(-), Gallstones(-)	667 (69.6)	667 (73.9)	52 (14.1)	1.0 -	55 (28.8)	1.0 -	28 (41.2)	1.0 -
Family History(+), Gallstones(-)	68 (7.1)	68 (7.5)	8 (2.2)	1.4 (0.6 - 3.1)	9 (4.7)	1.4 (0.6 - 2.9)	4 (5.9)	1.4 (0.5 - 4.2)
Family History(-), Gallstones(+)	201 (21.0)	153 (17.0)	245 (66.6)	21.1 (14.8 - 30.1)	107 (56.0)	7.6 (5.2 - 11.1)	30 (44.1)	4.0 (2.3 - 7.0)
Family History(+), Gallstones(+)	23 (2.4)	14 (1.6)	63 (17.1)	57.7 (30.2 - 110.5)	20 (10.5)	11.9 (6.0 - 23.5)	6 (8.8)	6.8 (2.5 - 18.4)
P interaction				*0.18*		*0.94*		*0.77*

[1] Population controls compared with bile duct and ampulla vater cancer cases

[2] Population controls without cholesectomy compared with gallbadder cancer cases

[3] Adjusted for age and gender