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Medical history and the risk of biliary tract cancers in Shanghai, China: implications for a role of inflammation

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Abstract

Several lines of evidence suggest that inflammation may play a role in the etiology of biliary tract cancers. To examine further the role of inflammation, we evaluated the associations between self-

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reported inflammatory-related medical conditions and the risk of biliary tract cancers in a population-based case-control study in Shanghai, China. Our analysis included 368 gallbladder cancer cases, 191 bile duct cancer cases, 68 ampulla of Vater cancer cases, and 959 healthy subjects. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for biliary tract cancers in relation to six inflammation-related conditions. Gallbladder cancer was significantly associated with cholecystitis occurring at least 5 years prior to interview (OR = 1.7, 95% CI 1.1–2.9). Even though biliary stones did not significantly modify the associations between cholecystitis and gallbladder cancer, 90% of the gallbladder cancer cases with cholecystitis also had biliary stones, indicating that stones likely play an important role in the link between cholecystitis and gallbladder cancer. Among subjects who smoked and drank alcohol, a history of gastric (OR = 4.3, 95% CI 1.2–15.0) or duodenal ulcers (OR = 3.7, 1.2–12.0) was associated with an excess risk of gallbladder cancer. Although the mechanisms are unclear, our results further support the role for inflammation in the etiology of biliary tract cancers.

Keywords

Biliary tract cancer; Biliary stones; Medical history; Inflammation; China

Introduction

Biliary tract cancers, encompassing tumors of the gallbladder, extrahepatic bile duct, and ampulla of Vater, are rare yet highly fatal malignancies [1]. Several lines of evidence suggest a role for inflammation in the etiology of biliary tract cancers [1]. For example, gallstones, which are the most important known risk factor for all three biliary tract cancer subsites, cause gallbladder hypomotility and biliary stasis, thereby increasing exposure to biliary carcinogens and chronic inflammation of the biliary tree [2, 3]. Closely related to gallstones, obesity, hyperlipidemia, diabetes, and metabolic syndrome, may also exert inflammatory effects that contribute to biliary tract cancer, especially gallbladder cancer [4–9]. Infectious agents, such as, *Helicobacter pylori* (*H. pylori*), *Salmonella typhi*, hepatitis B and C, and liver flukes are thought to initiate inflammatory reactions in the gastrointestinal and biliary tracts that may lead to carcinogenesis [1, 10–12]. Furthermore, inflammatory conditions of the biliary tree and gastrointestinal system, such as cholecystitis, primary sclerosing cholangitis, and ulcerative colitis have also been linked with the development of biliary tract malignancies, with the latter two conditions being more closely linked to bile duct cancer [1, 13–15]. Although the risk factors and mechanisms may vary by cancer subsite, inflammation appears to play a role in biliary tract carcinogenesis, possibly by increasing nitric oxide, leading to oxidative stress and DNA damage [1, 13–18].

To further examine the role of inflammation in biliary tract cancers, we evaluated the associations between several inflammatory-related medical conditions, including cholecystitis (inflammation of the gallbladder), pancreatitis (inflammation of the pancreas), appendicitis (inflammation of the appendix), chronic gastritis (inflammation of the lining of the stomach), gastric ulcer (erosion in the stomach), duodenal ulcer (erosion in the small intestine), and the risk of biliary tract cancers. This study was conducted within a large

population-based case-control study in Shanghai, China, where the incidence rates of biliary tract cancer has increased rapidly during recent decades.

Methods

Study subjects

Methods of this study have been previously published [3, 6–9, 12]. In this population-based case-control study among Shanghai residents, we included 627 incident biliary tract cancer cases (368 gallbladder, 191 extrahepatic bile duct (referred to as bile duct), 68 ampulla of Vater) between 35 and 74 years of age at diagnosis (1997–2001). Patients newly diagnosed with primary biliary tract cancers (ICD9 code 156) were recruited using a rapid-reporting system in 42 hospitals in Shanghai. More than 95% of incident biliary tract cancer patients in Shanghai were recruited. Biliary tract cancer cases were confirmed by histopathologic assessment (70%) or by an expert panel using medical and surgical records (30%). We also included 959 healthy subjects without a history of biliary tract cancer who were randomly selected from the Shanghai Resident Registry, and were frequency matched to cancer cases on gender and age (5-year intervals). Biliary stone status was assessed in nearly all biliary tract cancer cases and population controls using self-reported history and medical and surgical records.

Interview

Study subjects were interviewed in-person by trained interviewers using a structured questionnaire to obtain information on demographic characteristics, lifestyle behaviors, and medical histories. Cancer cases were interviewed within 3 weeks after diagnosis. The response rate for interviews was over 95% for cases and 82% for controls. Five percent of subjects were randomly reinterviewed within 3 months of the first interview; the concordance between key questions on the two interviews was greater than 90%.

Statistical analysis

The following case-control comparisons were made: gallbladder cancer cases were compared to controls without a history of cholecystectomy ($n = 902$); and bile duct and ampulla of Vater cancer cases were compared to all population controls regardless of stone or cholecystectomy status ($n = 959$). Associations between the medical conditions and the three biliary tract cancer sites were assessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. We examined medical conditions that were diagnosed prior to interview, and to account for the possibility that biliary diseases were causing these medical conditions, we also examined conditions that occurred at least 5 and 10 years prior to interview. To reduce the possibility of a joint effect of more than one medical condition, we also examined associations for participants who only had a history of one medical condition. The final regression model included factors that accounted for at least a 10% change in risk estimates; for gallbladder cancer we adjusted for gender, age, education, hypertension, and gallstones; and for bile duct cancer we adjusted for gender, age, hypertension, and gallstones. The likelihood ratio test was used to evaluate the interactions between the medical conditions and potential modifying factors (i.e., gender,

BMI, diabetes, hypertension, ever drink alcohol, smoking status, aspirin use, and stone status).

Results

Compared to controls, gallbladder cancer cases were more likely to be women, while bile duct cancer cases were slightly more likely to be men (Supplemental Table 1). Bile duct cancer cases were more likely than controls to have ever smoked cigarettes. Gallbladder cancer cases were less likely to drink alcohol, more likely to have a higher BMI (23 kg/m^2), and more likely to be diabetic than controls. Bile duct cancer cases were less likely to be hypertensive than controls. All cancer subtypes were more likely to have gallstones than controls.

Table 1 shows the association of selected medical conditions with gallbladder and bile duct cancer. As shown, 36.9% of the gallbladder cancer cases and 8% of the controls reported a history of cholecystitis, yielding a 3.4-fold risk (95% CI = 2.3–5.0), after adjustment for gender, age, education, hypertension, and stone status. When we limited the analysis to those with cholecystitis diagnosed at least 5 and 10 years prior to gallbladder cancer (14.9% of the cases vs. 4.8% of the controls), there was a 1.7-fold (95% CI 1.1–2.9) and a 2.3-fold (95% CI 1.2–4.1) risk of gallbladder cancer, respectively. Furthermore, when we excluded subjects who had at least one of the other medical conditions examined, subjects who only had cholecystitis prior to interview had a 4.6-fold (95% CI 2.7–7.9) risk of gallbladder cancer, but the association was attenuated when cholecystitis occurred at least 5 years prior to the interview (OR = 1.8, 95% CI 0.9–3.5). Pancreatitis occurring anytime prior to interview was associated with a nonsignificant twofold risk of gallbladder cancer (OR = 2.2, 95% CI 0.8–6.2). Chronic gastritis was inversely associated with gallbladder cancer, but only significantly for participants with chronic gastritis occurring 5 years prior to interview (OR = 0.6, 95% CI 0.4–0.9). None of the other medical conditions were significantly associated with gallbladder cancer.

For bile duct cancer, cholecystitis occurring any time prior to interview was significantly associated with a 2.2-fold risk (95% CI 1.4–3.5), adjusting for gender, age, hypertension, and stone status. This association was attenuated when we limited the analysis to participants with cholecystitis occurring at least 5 years (OR = 1.7, 95% CI 1.0–3.1) and 10 years prior to interview (OR = 1.7, 95% CI 0.9–3.5). Also, when excluding subjects with other medical conditions, cholecystitis was not significantly associated with bile duct cancer (OR = 1.6, 95% CI 0.8–3.2) and null for cholecystitis occurring 5 years prior to interview (OR = 0.9, 95% CI 0.4–2.2). Pancreatitis occurring anytime prior to interview was associated with a 2.5-fold risk (95% CI = 1.1–5.6). We did not have enough subjects to evaluate pancreatitis occurring 5 years prior to interview or independent of the other medical conditions. None of the other medical conditions were significantly associated with bile duct cancer.

For ampulla of Vater cancer, pancreatitis occurring anytime prior to interview was associated with a 5-fold risk (95% CI = 1.75–14.46) (Supplemental Table 2). We did not have enough subjects to evaluate pancreatitis occurring 5 years prior to interview or independent of the

other medical conditions. None of the other medical conditions were significantly associated with ampulla of Vater cancer.

Stratified analyses showed that alcohol drinking and smoking significantly modified the associations between gastric and duodenal ulcers on gallbladder cancer risk (Table 2). Gastric ulcer occurring anytime prior to interview was associated with a 3.9-fold risk (95% CI 1.3–12.5; p -interaction = 0.001) among subjects who drank alcohol, a 1.4-fold risk (95% CI 0.6–3.1; p -interaction = 0.03) among subjects who ever smoked, and a 4.3-fold risk (95% CI 1.2–15.0; p -interaction = 0.01) among subjects who both smoked and drank alcohol, while the associations were inverse or null for subjects who never drank alcohol or never smoked, respectively. Similarly, duodenal ulcer occurring anytime prior to interview was associated with a 3.4-fold risk (95% CI 1.1–10.5; p -interaction = 0.01) among subjects who drank alcohol, a 1.4-fold risk (95% CI 0.6–3.2; p -interaction = 0.13) among subjects who ever smoked, and a 3.7-fold risk (95% CI 1.2–12.0; p -interaction = 0.01) among subjects who drank alcohol and smoked, while the associations were null among subjects who never drank alcohol or never smoked. We found no evidence of a modifying effect of the other factors for which we had a sufficient number of subjects (> 5) to evaluate. Although biliary stones did not significantly modify the associations between the six inflammatory-related medical conditions and biliary tract cancers, we show the stratified results (Supplemental Table 3) given the importance of biliary stones as a risk factor for biliary tract cancers.

Discussion

In this population-based case-control study in Shanghai, China, we examined the associations between six inflammatory-related medical conditions on the risks of gallbladder and bile duct cancers. Of the medical conditions examined, cholecystitis was the strongest risk factor for biliary tract cancers. Gastric and duodenal ulcers were also significantly associated with higher risks of gallbladder cancer, but the effect was limited to subjects who smoked or drank alcohol.

Cholecystitis is an inflammation of the gallbladder that is usually caused by an obstruction of the cystic duct, typically by gallstones [19]. In our study, cholecystitis was associated with excess risks of gallbladder and bile duct cancers. Among gallbladder cancer cases with cholecystitis, 59% reported having their cholecystitis diagnosed within the four years prior to cancer diagnosis (and mostly within the first year), suggesting that most cholecystitis among cancer cases could have resulted from recent tumor obstruction or, possibly, biliary stones, since over 85% of the cancer cases with cholecystitis also had stones. Biliary stone status did not significantly modify the association between cholecystitis and gallbladder cancer risk; however, we had a limited number of gallbladder cancer cases with cholecystitis and without stones, and too few subjects in this group to evaluate cholecystitis occurring 5 or more years prior to interview.

While previous studies have reported an association between cholecystitis and gallbladder cancer [13, 20, 21], the temporal relationship between the conditions is not clear, nor is the role of biliary stones. Our results, together with existing literature, suggest that, in most cases, biliary stones likely play an important role in the link between cholecystitis and

biliary tract cancers via inflammatory processes. Although the mechanisms are unclear, chronic inflammation from cholecystitis and biliary stones may produce cytokines and nitric oxide, which have been shown to induce DNA damage [16] or suppress the immune system by inhibiting lymphocyte proliferation [22]. In turn, these factors may play a role in the development or progression of biliary tract cancers [12, 13, 23, 24]. Furthermore, a previous study conducted in our population reported that common variants in genes that influence inflammatory responses may predispose to biliary stones and biliary tract cancer, providing additional support for a role of inflammation in biliary tract carcinogenesis [25].

The increased risk of gallbladder cancer in relation to gastric and duodenal ulcers among subjects who smoked or drank alcohol is intriguing, but needs confirmation. In our study population, smoking and alcohol drinking are less common among gallbladder cancer cases, but more common in bile duct cancer cases than controls. Smoking and alcohol drinking are risk factors for gastric and duodenal ulcers as they promote the movement of bile salts from the intestine to the stomach, and increase the amount of acid produced by the stomach [26, 27]. Smoking may also increase the risk of infection with *H. pylori* [28], which is a strong risk factor for peptic ulcers (gastric or duodenal ulcers) [26]; and has been linked to biliary tract cancers [1]. Thus, it appears biologically plausible that the combined effects of increased acid production from smoking and alcohol drinking, together with the chronic inflammation from ulcer, and possibly *H. pylori* infection, could increase the risk of gallbladder cancer. To note, approximately 75% of the controls reported a history of *H. pylori* infection. We found no association between *H. pylori* and biliary tract cancer risk, nor did *H. pylori* modify the effects of gastric or duodenal ulcers, however, we did not have information of diagnosis date or treatment for *H. pylori*. Previous studies of ulcers and biliary tract cancers are scarce, although one international multi-center study reported a threefold risk of gallbladder cancer among persons with previous surgical treatment for peptic ulcer (gastric or duodenal) [29].

Strengths of this study include the relatively large size, and minimal selection bias due to the high response rate, population-based design, and minimal misclassification of biliary disease with the detailed cancer status confirmation. We also were able to evaluate the impact of potential confounding and modifying factors such as biliary stones, given the nearly complete assessment of stones among the cancer cases. As a limitation, we had limited occupational data to consider potential confounding by occupational exposures, but since participants were selected from the general population we do not have subjects with high occupational exposures, so confounding, if any, should be minimal. The case-control design limited our ability to assess the temporal relationship between the medical conditions and biliary diseases. To minimize the impact of reverse causation, we excluded subjects with medical conditions that were diagnosed in the preceding 5 or 10 years prior to the diagnosis of stone or cancer. Since the medical conditions evaluated here were based on self-report without medical record validation, misclassification due to recall is possible, although likely not differential between cases and controls. Also, self-reported medical conditions are usually more severe conditions that require medical attention, thus asymptomatic conditions would likely not be included; this may or may not be differential in cases and controls.

In summary, our study showed an increased risk of biliary tract cancer associated with cholecystitis, as well as an increased risk of gallbladder cancer among smokers and drinkers who had a history of gastric and duodenal ulcer. These findings, together with previous findings from other studies, suggest that biliary stones may play a role in the development of these medical conditions, particularly cholecystitis, which in turn contribute to increased risk of biliary tract cancers, especially gallbladder cancer, via inflammatory-induced mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Odds ratios (ORs) and 95% confidence intervals (95% CI) for biliary stones and cancers in relation to medical conditions

Medical conditions	Controls ^a			Stone cases ^a			Controls ^b			Gallbladder cancer ^b			Controls ^c			Bile duct cancer ^c		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
All subjects	735			981	–	–	902			368	–	–	959			191	–	–
Cholecystitis																		
No	693			485	1.0	–	829			232	1.0	–	875			143	1.0	–
Yes—prior to biliary disease ^d	42			39	1.4	0.9–2.2	73			136	3.4	2.3–5.0	84			48	2.2	1.4–3.5
Yes—5 years prior ^e	18			27	2.3	1.2–4.3	43			55	1.7	1.1–2.9	49			24	1.7	1.0–3.1
Yes—10 years prior ^f	4			15	–	–	29			42	2.3	1.2–4.1	32			16	1.7	0.9–3.5
Cholecystitis without other medical conditions																		
No	404			216	1.0	–	483			140	1.0	–	499			87	1.0	–
Yes—prior to biliary disease ^d	18			18	2.2	1.1–4.5	32			80	4.6	2.7–7.9	36			18	1.6	0.8–3.2
Yes—5 years prior ^e	10			11	2.6	1.0–6.6	23			32	1.8	0.9–3.5	25			8	0.9	0.4–2.2
Pancreatitis																		
No	730			893	1.0	–	893			351	1.0	–	944			178	1.0	–
Yes—prior to biliary disease ^d	5			86	13.6	5.4–33.9	9			17	2.2	0.8–6.2	15			13	2.4	1.1–5.6
Yes—5 years prior ^e	5			4	–	–	9			1	–	–	15			3	–	–
Yes—10 years prior ^f	5			4	–	–	9			1	–	–	15			3	–	–
Appendicitis																		
No	601			772	1.0	–	743			307	1.0	–	781			163	1.0	–
Yes—prior to biliary disease ^d	134			183	1.1	0.9–1.5	159			61	1.0	0.8–1.6	178			28	0.7	0.4–1.1
Yes—5 years prior ^e	124			166	1.1	0.9–1.5	149			50	0.9	0.6–1.4	167			23	0.6	0.3–1.0
Yes—10 years prior ^f	116			145	1.1	0.8–1.4	140			49	0.9	0.6–1.4	158			22	0.6	0.4–1.0
Appendicitis without other medical conditions																		
No	404			216	1.0	–	483			140	1.0	–	499			87	1.0	–
Yes—prior to biliary disease ^d	79			44	1.2	0.8–1.9	85			22	1.2	0.7–2.3	92			10	0.6	0.3–1.3

Medical conditions	Controls ^a			Stone cases ^a			Controls ^b			Gallbladder cancer ^b			Controls ^c			Bile duct cancer ^c		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
Yes—5 years prior ^e	73			37	1.2	0.8–1.9	79			19	1.1	0.6–2.2	86			8	0.5	0.2–1.2
Chronic Gastritis																		
No	574			702	1.0	–	703			295	1.0	–	737			146	1.0	–
Yes—prior to biliary disease ^d	161			164	1.0	0.8–1.3	199			73	0.8	0.6–1.2	222			45	0.9	0.6–1.3
Yes—5 years prior ^e	126			113	0.9	0.7–1.2	155			41	0.6	0.4–0.9	170			29	0.8	0.5–1.3
Yes—10 years prior ^f	100			77	0.8	0.5–1.1	123			35	0.6	0.4–1.0	137			24	0.7	0.4–1.2
Chronic Gastritis without other medical conditions																		
No	404			216	1.0	–	483			140	1.0	–	499			87	1.0	–
Yes—prior to biliary disease ^d	88			42	1.1	0.7–1.7	107			24	0.7	0.4–1.2	112			12	0.6	0.3–1.1
Yes—5 years prior ^e	61			27	1.0	0.6–1.7	75			12	0.5	0.2–1.0	79			8	0.5	0.2–1.1
Gastric Ulcer																		
No	676			904	1.0	–	823			337	1.0	–	875			175	1.0	–
Yes—prior to biliary disease ^d	59			49	0.8	0.5–1.1	79			31	0.8	0.4–1.3	84			16	0.8	0.5–1.6
Yes—5 years prior ^e	50			39	0.7	0.5–1.2	67			19	0.6	0.3–1.0	70			12	0.8	0.4–1.6
Yes—10 years prior ^f	38			29	0.8	0.5–1.3	52			15	0.5	0.3–1.1	54			9	0.7	0.3–1.6
Gastric Ulcer without other medical conditions																		
No	404			216	1.0	–	483			140	1.0	–	499			87	1.0	–
Yes—prior to biliary disease ^d	16			8	1.3	0.5–3.2	20			8	1.0	0.4–2.9	21			8	1.7	0.7–4.3
Yes—5 years prior ^e	11			6	1.6	0.5–4.6	15			6	0.9	0.3–2.9	16			6	1.5	0.5–4.2
Duodenal Ulcer																		
No	672			868	1.0	–	819			334	1.0	–	870			171	1.0	–
Yes—prior to biliary disease ^d	63			78	1.1	0.8–1.6	83			34	0.9	0.5–1.5	89			20	0.8	0.5–1.4
Yes—5 years prior ^e	58			64	1.0	0.7–1.5	76			22	0.6	0.3–1.1	79			12	0.6	0.3–1.2
Yes—10 years prior ^f	48			52	1.0	0.7–1.5	65			19	0.6	0.3–1.0	68			11	0.6	0.3–1.3
Duodenal Ulcer without other medical conditions																		
No	404			216	1.0	–	483			140	1.0	–	499			87	1.0	–

Medical conditions	Controls ^a		Stone cases ^a		Controls ^b		Gallbladder cancer ^b		Controls ^c		Bile duct cancer ^c	
	n	OR	n	OR	n	OR	n	OR	n	OR	n	OR
Yes—prior to biliary disease ^d	26	1.3	18	1.3	37	0.6–2.5	6	0.4	37	0.2–1.1	5	0.5
Yes—5 years prior ^e	25	1.0	14	1.0	35	0.5–2.1	6	0.5	35	0.2–1.3	3	–

^aBiliary stone cases compared to controls without stones (*n* = 735); adjusted for gender, age, ever drink alcohol, body mass index, diabetes, hypertension

^bGallbladder cancer cases compared to controls without cholecystectomy (*n* = 902); adjusted for gender, age, education, hypertension, stones

^cBile duct cancer cases compared to all controls (*n* = 959); adjusted for gender, age, hypertension, stones

^dMedical condition was diagnosed prior to stone diagnosis for biliary stone risk estimates or prior to interview for cancer risk estimates

^eMedical condition was diagnosed at least 5 years prior to stone diagnosis for biliary stone risk estimates or 5 years prior to interview for cancer risk estimates

^fMedical condition was diagnosed at least 10 years prior to stone diagnosis for biliary stone risk estimates or 10 years prior to interview for cancer risk estimates

Table 2

Odds ratios (ORs) and 95% confidence intervals (95% CI) for gallbladder cancer in relation to gastric and duodenal ulcers by alcohol drinking and smoking status

Medical histories	Controls ^a			Gallbladder Cancer ^a			Controls ^a			Gallbladder cancer ^a			Controls ^a			Gallbladder Cancer ^a		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI			
	Never drink alcohol						Ever drink alcohol						Never smoke					
	Ever smoke						Never smoke						Ever smoke					
All subjects	715	316	–	186	52	–	633	278	–	269	89	–						
Gastric ulcer																		
No	658	297	1.0	165	40	1.0	585	267	1.0	238	69	1.0	–					
Yes—prior to biliary disease ^b	57	19	0.5	0.3–0.9	21	12	3.9	1.3–12.5	48	11	0.4	0.2–0.9	31	20	1.4	0.6–3.1		
<i>p</i> -interaction							0.001						0.03					
Duodenal ulcer																		
No	657	294	1.0	162	40	1.0	582	259	1.0	237	74	1.0	–					
Yes—prior to biliary disease ^b	58	22	0.6	0.3–1.1	24	12	3.4	1.1–10.5	51	19	0.6	0.3–1.3	32	15	1.4	0.6–3.2		
<i>p</i> -interaction							0.01						0.13					
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	Never drink alcohol and never smoke						Ever drink alcohol and ever smoke						Ever drink alcohol and ever smoke					
All subjects	577	263		138	52		55	15		131	37							
Gastric ulcer																		
No	536	253	1.0	122	43	1.0	49	14	1.0	116	26	1.0	–					
Yes—prior to biliary disease ^b	41	10	0.4	0.2–0.8	16	9	0.7	0.2–2.2	6	1	–	–	15	11	4.3	1.2–15.0		
<i>p</i> -interaction													0.01					
Duodenal ulcer																		
No	532	244	1.0	125	49	1.0	50	15	1.0	112	25	1.0	–					
Yes—prior to biliary disease ^b	45	19	0.6	0.3–1.3	13	3	–	5	0	–	12	3.7	1.2–12.0					
<i>p</i> -interaction													0.01					

^aGallbladder cancer cases compared to controls without cholecystectomy ($n = 902$); adjusted for gender, age, education, hypertension, stones

^bCancer cases and respective controls were diagnosed with medical conditions prior to interview