



Original Contribution

Gallstones, Cholecystectomy, and Risk of Digestive System Cancers

Leticia Nogueira*, Neal D. Freedman, Eric A. Engels, Joan L. Warren, Felipe Castro, and Jill Koshiol

* Correspondence to Dr. Leticia Nogueira, National Cancer Institute, 9609 Medical Center Drive, MSC 7248, Bethesda, MD 20892 (e-mail: leticia.nogueira@nih.gov).

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Gallstones and cholecystectomy may be related to digestive system cancer through inflammation, altered bile flux, and changes in metabolic hormone levels. Although gallstones are recognized causes of gallbladder cancer, associations with other cancers of the digestive system are poorly established. We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (1992–2005), which includes 17 cancer registries that cover approximately 26% of the US population, to identify first primary cancers ($n = 236,850$) occurring in persons aged ≥ 66 years and 100,000 cancer-free population-based controls frequency-matched by calendar year, age, and gender. Odds ratios and 95% confidence intervals were calculated using logistic regression analysis, adjusting for the matching factors. Gallstones and cholecystectomy were associated with increased risk of noncardia gastric cancer (odds ratio (OR) = 1.21 (95% confidence interval (CI): 1.11, 1.32) and OR = 1.26 (95% CI: 1.13, 1.40), respectively), small-intestine carcinoid (OR = 1.27 (95% CI: 1.01, 1.60) and OR = 1.78 (95% CI: 1.41, 2.25)), liver cancer (OR = 2.35 (95% CI: 2.18, 2.54) and OR = 1.26 (95% CI: 1.12, 1.41)), and pancreatic cancer (OR = 1.24 (95% CI: 1.16, 1.31) and OR = 1.23 (95% CI: 1.15, 1.33)). Colorectal cancer risk associated with gallstones and cholecystectomy decreased with increasing distance from the common bile duct (P -trend < 0.001). Hence, gallstones and cholecystectomy are associated with the risk of cancers occurring throughout the digestive tract.

cancer; cholecystectomy; digestive system; gallstones; gastric cancer; liver; pancreas

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-O, *International Classification of Diseases for Oncology*; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

Digestive system cancers include cancers of the esophagus, stomach, small intestine, colon, and rectum, as well as cancers of the liver, gallbladder, bile duct, and pancreas, and are estimated to have accounted for approximately 290,000 new diagnoses and over 140,000 deaths in the United States in 2013 (1). In developing countries, cancers of the digestive system are among the 5 most commonly diagnosed cancers in both men and women (2). Identification of risk factors for digestive system cancers may help in developing targets and strategies for cancer prevention and early detection.

Gallstones are strongly associated with increased risk of biliary tract cancers (3, 4), but their association with digestive system cancers outside of the biliary tract is not well established. In 2009, gallstones were the second most common gastrointestinal discharge diagnosis among US hospitalizations, accounting for over 300,000 physician visits that year

(5). Gallstones can lead to inflammation of the gallbladder, the biliary tract ducts, the liver, and the pancreas (6). The link between inflammation and cancer is well-established (7); hence, gallstones could increase the risk of a number of different digestive system cancers (8). Although cholecystectomy can ameliorate the inflammatory state associated with gallstones (9), it may also increase the exposure of the small intestine, stomach, and esophagus to bile (10) and change metabolic hormone levels (11), which might affect cancer risk in digestive system organs.

We evaluated the associations of gallstones and cholecystectomy with digestive tract cancers in a large, population-based case-control study. Based on the biological mechanisms described above, we hypothesized that gallstones and/or cholecystectomy would be associated with increased risk of digestive system cancers, including cancers of the adjacent

organs of the liver, pancreas, and small intestine. We also explored associations with cancers of the esophagus, stomach, colon, and rectum.

METHODS

Data source and study population

We conducted a case-control study within the US elderly population (persons aged ≥ 65 years) using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data. The SEER data come from registries that collect information about all incident cancers occurring in defined geographical areas representing 26% of the US population. Patients in SEER have been linked to Medicare enrollment data; approximately 94% of SEER patients aged 65 years or older have been linked to Medicare enrollment records. For these linked patients, Medicare data include patient demographic information (age, gender, and race). Medicare claims are submitted from hospitals, outpatient facilities, and treating physicians from the time of Medicare enrollment to death or enrollment in a health maintenance organization. Each patient's Medicare claims have codes for specific diagnoses and procedures, as previously described (12). To guarantee at least 12 months between exposure and cancer diagnosis/selection, cases were required to be aged 66 years or older and were defined as persons with first primary cancers occurring between 1992 and 2005. A lag time of at least 12 months is important in order to ensure evaluation of incident cancers and avoid selection of cases who might have been assessed for the exposures of interest because they were ill from incipient cancer. Persons who were diagnosed with cancer only at autopsy or by death certificate were excluded, since these cancers may have atypical clinical features (13).

We randomly selected 100,000 cancer-free population-based controls from a 5% subcohort representing a random sample of Medicare recipients residing in the SEER areas, frequency-matched to cases by calendar year of selection, age, and gender. Controls were cancer-free at the time of selection and had prior Medicare coverage for at least 12 months before selection.

Assessment of cancer cases

Cancers were identified by anatomical site and *International Classification of Diseases for Oncology* (ICD-O) histological code. The ICD-O codes for anatomical site were C15.0–C15.9 for esophageal cancer, C16.0–C16.9 for gastric cancer (C16.0 for gastric cardia cancer and C16.1–C16.7 for gastric noncardia cancer), C17.0–C17.9 for small-intestine cancer, C18.0 and C18.2–C18.4 for proximal colon cancer, C18.5–C18.7 for distal colon cancer, C19.9 and C20.9 for rectal cancer, C23.0–C23.9 for gallbladder cancer, C24.1 for ampulla of Vater cancer, C22.0 for liver cancer, and C25.0–C25.9 for pancreatic cancer. Histological codes included ICD-O codes 8050–8089 for esophageal squamous-cell carcinoma; ICD-O codes 8140–8150, 8190–8231, 8260–8263, 8310, 8331, 8430–8522, 8525, 8530, 8550, 8551, and 8576 for esophageal and small-intestine adenocarcinomas; and ICD-O codes 8013, 8240–8244, and 8246–8249 for small-intestine carcinoid.

Table 1. Demographic Characteristics of Participants in the SEER-Medicare Study, 1992–2005

	Controls (n = 100,000)		All Cancers (n = 1,138,390)	
	No.	%	No.	%
Mean age, years	76.5 (6.9) ^a		76.5 (6.8)	
Gender				
Male	53,086	53.1	604,333	53.1
Female	46,914	46.9	534,057	46.9
Race/ethnicity ^b				
White	83,433	85.9	973,236	87.6
Black	7,028	7.2	89,893	8.1
Asian	4,032	4.2	18,286	1.6
Hispanic	2,567	2.6	29,038	2.6

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

^a Numbers in parentheses, standard deviation.

^b Numbers do not sum to totals because of missing data.

Exposure assessment

Participants in our study were defined as having gallstones if they had received a hospital, outpatient, or physician *International Classification of Diseases, Ninth Revision* (ICD-9), claim code of 574.xx at least 12 months prior to cancer diagnosis or control selection. Similarly, participants were defined as having undergone cholecystectomy if they had received a hospital ICD-9 procedure code of 51.2x or a physician or outpatient claim with a *Current Procedural Terminology, Fourth Edition*, code for cholecystectomy (codes 47562, 47563, 47564, 56340, 56341, and 56342) at least 12 months prior to cancer diagnosis or control selection. Gallstone exposure was defined as having had at least 1 claim for gallstones and no cholecystectomy claims. Cholecystectomy exposure was defined as ever having had a cholecystectomy claim. Diabetes was identified from physician and hospital claims using ICD-9 codes 250x, 357.2, 362.0x, and 366.41.

Statistical analysis

The association between claims for gallstones or cholecystectomy and cancer risk was assessed using unconditional logistic regression analysis with adjustment for matching factors and duration of Medicare benefits coverage. Odds ratios with 95% confidence intervals were calculated to assess the strength of the association between gallstones or cholecystectomy and each cancer site. For cancers for which diabetes is a well-established risk factor (e.g., liver, pancreas, gallbladder, and colorectum), odds ratios with 95% confidence intervals were also calculated while adjusting for the presence of diabetes. The odds ratio variance estimates were adjusted for the fact that a control could be sampled more than once in multiple calendar years or could later become a case. We adjusted for multiple comparisons with the total number of digestive system cancers defined by SEER (14) using the Bonferroni method ($P < 0.002$).

Table 2. Association of Gallstones and Cholecystectomy With Digestive System Cancers in the SEER-Medicare Study, 1992–2005

Cancer	Total No. of Participants	Gallstones					Cholecystectomy				
		No. of Cases	%	OR	95% CI	P Value	No. of Cases	%	OR	95% CI	P Value
Esophageal	11,442	464	4.1	1.06	0.96, 1.18	0.23	270	2.4	0.94	0.82, 1.06	0.23
Squamous-cell carcinoma	4,732	203	4.3	1.15	1.00, 1.33	0.05	100	2.1	0.85	0.69, 1.04	0.12
Adenocarcinoma	5,488	220	4.0	1.05	0.91, 1.21	0.49	132	2.4	0.95	0.80, 1.14	0.59
Gastric	22,860	1,127	4.9	1.15	1.08, 1.24	<10 ⁻⁴	684	3.0	1.15	1.05, 1.26	0.001
Cardia	5,579	213	3.8	0.96	0.84, 1.11	0.62	122	2.2	0.88	0.73, 1.06	0.18
Noncardia	12,925	687	5.3	1.21	1.11, 1.32 ^a	<10 ⁻⁵	429	3.3	1.26	1.13, 1.40 ^a	<10 ⁻⁴
Small intestine	3,694	183	5.0	1.23	1.05, 1.43	0.009	148	4.0	1.49	1.26, 1.77	<10 ⁻⁵
Adenocarcinoma	1,484	77	5.2	1.21	0.96, 1.53	0.10	55	3.7	1.34	1.02, 1.76	0.04
Carcinoid	1,630	79	4.8	1.27	1.01, 1.60	0.04	76	4.7	1.78	1.41, 2.25 ^a	<10 ⁻⁵
Colorectal	150,045	6,152	4.1	0.95	0.91, 0.99	0.10	3,907	2.6	0.97	0.92, 1.02	0.20
Proximal colon	66,740	3,072	4.6	1.00	0.95, 1.06	0.85	1,963	2.9	1.06	0.99, 1.12	0.08
Distal colon	40,996	1,604	3.9	0.94	0.89, 1.00	0.05	986	2.4	0.93	0.86, 1.00	0.05
Rectum	36,691	1,244	3.4	0.83	0.78, 0.89 ^a	<10 ⁻⁷	810	2.2	0.85	0.78, 0.92 ^a	<10 ⁻⁴
Auxiliary organs											
Gallbladder	3,664	468	12.8	3.13	2.82, 3.48 ^a	<10 ⁻⁹⁹	8	0.2	0.07	0.04, 0.15 ^a	<10 ⁻¹²
Ampulla of Vater	1,646	99	6.0	1.52	1.23, 1.87 ^a	<10 ⁻⁴	80	4.9	1.87	1.49, 2.36 ^a	<10 ⁻⁷
Liver	10,219	963	9.4	2.35	2.18, 2.54	<10 ⁻⁹⁹	332	3.2	1.26	1.12, 1.41	0.0001
Hepatocellular carcinoma	8,104	804	9.9	2.91	2.68, 3.16 ^a	<10 ⁻⁹⁹	273	3.4	1.34	1.17, 1.52 ^a	<10 ⁻⁴
Cholangiocarcinoma	3,681	275	7.5	1.83	1.61, 2.08 ^a	<10 ⁻¹⁵	118	3.2	1.19	0.98, 1.43	0.07
Pancreas	33,280	1,711	5.1	1.24	1.16, 1.31 ^a	<10 ⁻¹¹	1,106	3.3	1.23	1.15, 1.33 ^a	<10 ⁻⁷
All cancers	236,850	11,167	4.7				6,535	2.8			
Controls	100,000	3,930	3.9				2,572	2.6			

Abbreviations: CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

^a $P < 0.002$.

To identify changes in the association with increasing time from baseline, we evaluated the adjusted odds ratios across 4 time intervals: 13–30 months, 31–48 months, 49–72 months, and >72 months from gallstones diagnosis or cholecystectomy. We did not consider the period ≤ 12 months before cancer diagnosis or control selection to avoid surveillance bias (i.e., that diagnosis of gallstones or a cholecystectomy led to evaluation for cancer). The Wald χ^2 statistic was used to evaluate whether an increasing or decreasing trend in the odds ratio over time for each time interval existed.

RESULTS

The mean age of the population was 76.5 (standard deviation, 6.8) years (Table 1). The gender distribution was balanced: 53.1% male and 46.9% female in both cases and controls. The majority of the participants were white (85.9% of controls and 87.6% of cancer cases). A total of 236,850 cancer cases were included in the study, of whom 11,167 (4.7%) had Medicare claims for gallstones without subsequent cholecystectomy and 6,537 (2.8%) had claims for cholecystectomy. Among the 100,000 population controls, 3,930 (3.9%) had claims for gallstones and 2,572 (2.6%) had

claims for cholecystectomy between 1992 and 2005. The distributions of age, gender, and follow-up time for each cancer type are presented in Web Table 1 (available at <http://aje.oxfordjournals.org>).

As expected, gallstones were associated with increased risk of gallbladder cancer (adjusted (OR) = 3.13, 95% confidence interval (CI): 2.82, 3.48), while cholecystectomy was associated inversely (OR = 0.07, 95% CI: 0.04, 0.15). Both gallstones and cholecystectomy increased the risk of ampulla of Vater cancer (OR = 1.52 (95% CI: 1.23, 1.87) and OR = 1.87 (95% CI: 1.49, 2.36), respectively) (Table 2).

The association between gallstones and hepatocellular carcinoma appeared to be stronger (OR = 2.91, 95% CI: 2.68, 3.16) than the association with cholecystectomy (OR = 1.34, 95% CI: 1.17, 1.52), and cholangiocarcinoma demonstrated a similar pattern (OR = 1.83 (95% CI: 1.61, 2.08) and OR = 1.19 (95% CI: 0.98, 1.43), respectively) (Table 2). Gallstones and cholecystectomy were also associated with increased risk of pancreatic cancer (OR = 1.24 (95% CI: 1.16, 1.31) and OR = 1.23 (95% CI: 1.15, 1.33), respectively).

In addition, both gallstones (OR = 1.27, 95% CI: 1.01, 1.60) and cholecystectomy (OR = 1.78, 95% CI: 1.41, 2.25) were associated with increased risk of small-intestine

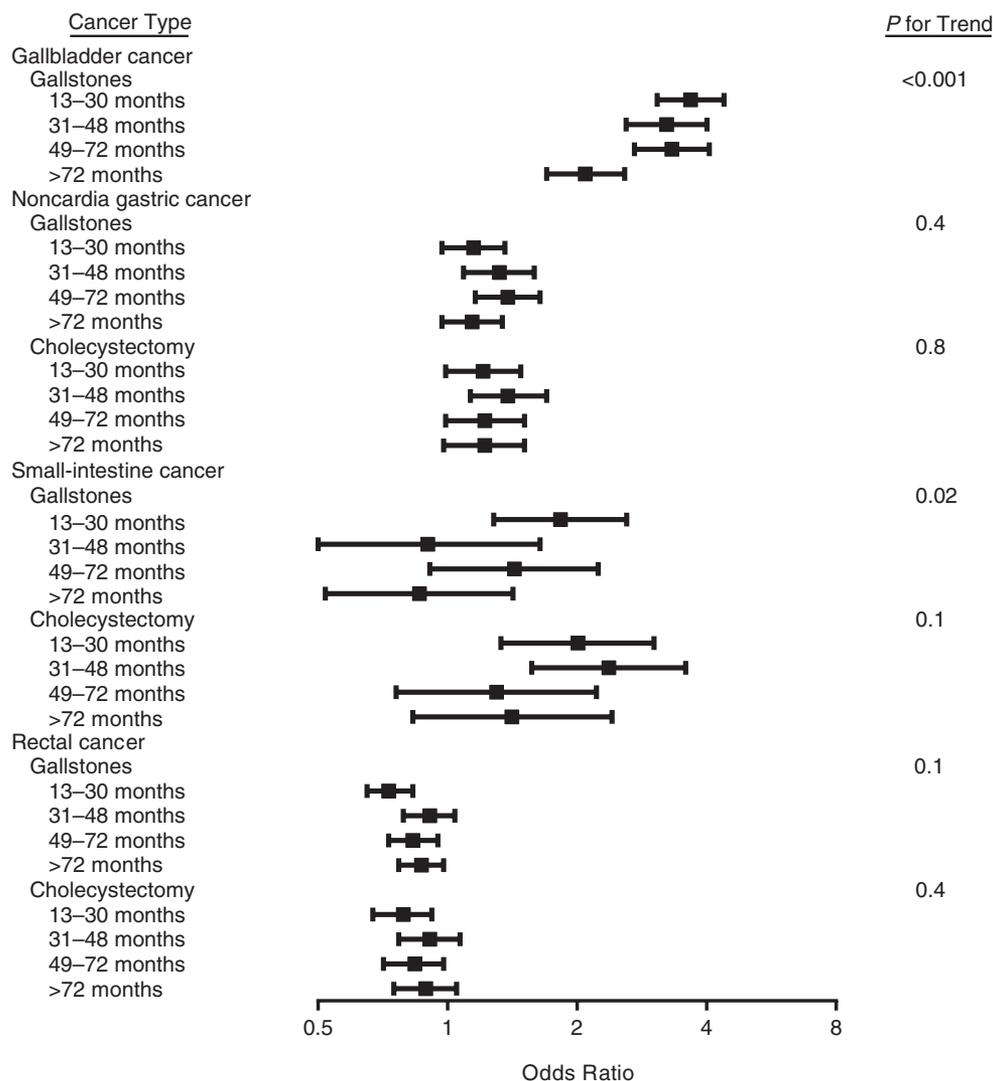


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carcinoid, but only the association of cholecystectomy with small-intestine carcinoid remained significant after Bonferroni correction (Table 2).

Gallstones and cholecystectomy were not associated with cancers of the proximal or distal colon, but they were inversely associated with rectal cancer (Table 2). The inverse associations of gallstones and cholecystectomy with colorectal cancer became stronger with increasing distance from the bile excretion site (P -trend < 0.001): Odds ratios declined from 1.00 (95% CI: 0.95, 1.06) and 1.06 (95% CI: 0.99, 1.12) in the proximal colon to 0.94 (95% CI: 0.89, 1.00) and 0.93 (95% CI: 0.86, 1.00) in the distal colon and 0.83 (95% CI: 0.78, 0.89) and 0.85 (95% CI: 0.78, 0.92) in the rectum (Table 2).

Finally, among other examined cancers, gallstones and cholecystectomy were associated with increased risk of non-cardia gastric cancer (OR = 1.21 (95% CI: 1.11, 1.32) and

OR = 1.26 (95% CI: 1.13, 1.40), respectively) but not with esophageal squamous-cell carcinoma, esophageal adenocarcinoma, or gastric cardia adenocarcinoma (Table 2). Associations did not change after adjustment for diabetes (Web Table 2).

Time between Medicare claim and cancer diagnosis

The associations between gallstones and some cancers (small intestine, gallbladder, ampulla of Vater, hepatocellular carcinoma, and cholangiocarcinoma) were stronger during the first 13–30 months after the gallstone claim and decreased with longer time intervals (P < 0.05). Even so, associations with hepatocellular carcinoma and with gallbladder, pancreas, and noncardia stomach cancers remained statistically significant for cancers occurring more than 6 years after a gallstone claim (Figure 1).

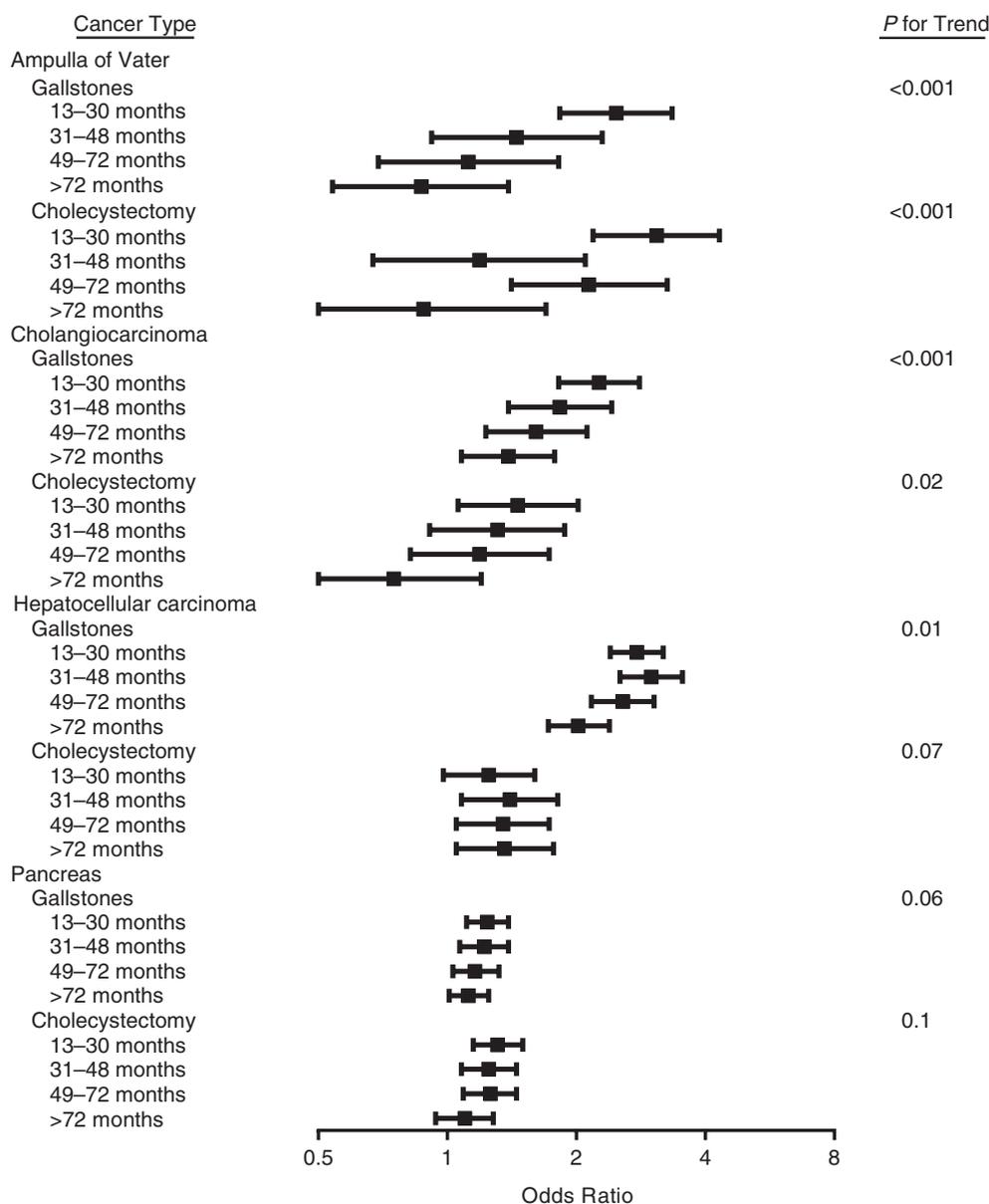


Figure 1. Trends in odds ratios for the associations of gallstones and cholecystectomy with digestive system cancers with increasing time between Medicare claim and cancer diagnosis in linked SEER-Medicare data, SEER-Medicare Study, 1992–2005. SEER, Surveillance, Epidemiology, and End Results. Bars, 95% confidence intervals.

For cholecystectomy, in contrast, only the associations with ampulla of Vater cancer and cholangiocarcinoma decreased significantly over time (Figure 1). There was no time trend for the associations between gallstones or cholecystectomy and noncardia gastric cancers, rectal cancers, and pancreatic cancers (Figure 1).

DISCUSSION

In this population-based US study, gallstones and cholecystectomy were associated with increased risk of several digestive system cancers in addition to biliary tract cancers,

including cancers of the stomach, liver (hepatocellular carcinoma and cholangiocarcinoma), pancreas, and small intestine. Within the colorectum, gallstones and cholecystectomy were associated with reduced risk of colorectal cancer with increasing distance from the common bile duct. In addition, risk estimates did not change after adjustment for diabetes, lending credibility to the observed associations, although we cannot exclude the possibility of confounding by other risk factors.

The association of cholecystectomy with noncardia gastric cancer and small-intestine carcinoid suggests that exposure to bile may be an important carcinogenic mechanism. Reflux of

the bile into the stomach is a common side effect of cholecystectomy (15) and has been shown to induce gastric adenocarcinomas in rats (16). Most previous studies of gallstones or cholecystectomy and gastric cancers were small and did not distinguish between cardia and noncardia cancers (17–19), but some found borderline-significant positive associations (20–22). One Swedish study of cholecystectomy and noncardia gastric cancers found a significant positive association (OR = 1.21, 95% CI: 1.10, 1.32) similar to that of our study (23).

The small intestine also becomes exposed to increased levels of bile acids after cholecystectomy (24). Bile exposure modifies intestinal mucosal morphology and stimulates epithelial cell proliferation (25, 26). A positive association of gallstones (21, 27) and cholecystectomy (28) with small-intestine cancer has been consistently reported in smaller studies, and in our study the association remained significant more than 6 years after diagnosis. Taken together, these findings support associations of gallstones and cholecystectomy with both noncardia gastric cancer and small-intestine cancer.

In the SEER-Medicare data, we observed a trend towards decreasing risk of colorectal cancer with increasing distance from the bile excretion site in association with gallstones and cholecystectomy claims. In addition to changes in bile flow, cholecystectomy also leads to changes in the composition of bile acids (29), which might have distinct effects on colon and rectal cancer risk (30). Some (21, 28, 31–45) but not all (20, 46–54) previous epidemiologic studies, including 2 meta-analyses evaluating the association of cholecystectomy with proximal and distal colon cancer (55, 56), have identified a trend pointing in the same direction as the one identified in the SEER-Medicare data.

In addition to its carcinogenic properties (28, 29, 57–59), bile can lead to inflammation when in contact with epithelial tissues outside of the gallbladder (60, 61). Both bile exposure and inflammation are among the several possible mechanisms that may link gallstones and cholecystectomy with cancer. While exposure of epithelial tissues to bile is a carcinogenic mechanism associated specifically with cholecystectomy, inflammation is a well-established carcinogenic mechanism (7) that is common to gallstones and cholecystectomy. Gallstones are known to cause inflammation in organs adjacent to the gallbladder (6, 62), while cholecystectomy can alleviate gallstone-related inflammation (9). Accordingly, although associations with cholangiocarcinoma decrease rapidly with time after cholecystectomy, they remain significantly elevated even 6 or more years after gallstone diagnosis (63, 64). Gallstones also seem to be associated with greater liver cancer risk than cholecystectomy (63–65). If they are not caused by chance, stronger associations of gallstones with liver cancer could be explained by increased surveillance of gallstone patients (21, 63, 64) or be confounded by other liver cancer risk factors (22, 63). While confounding is also a possible explanation for the association of cholecystectomy with liver cancer (63, 66, 67), an additional hypothesis is that removal of the gallbladder leads to accumulation of bile in the liver (68), where bile acids can act as carcinogens (69).

Inflammation might also play a role in the association of gallstones with pancreatic cancer, since gallstones can lead to pancreatitis (70), a known risk factor for pancreatic cancer (71–73). Not surprisingly, the association between gallstones

and pancreatic cancer identified in SEER-Medicare data has been extensively reported previously (21, 63, 74–79). In contrast to liver cancer, the association of pancreatic cancer with cholecystectomy was of similar magnitude as the association with gallstones, as previously reported (63, 75, 77, 80–82). Odds ratios for this association remained significant for more than 4 years following cholecystectomy in our study and other studies (81, 83–85). In addition to inflammation, associations for pancreatic cancer may be due to increased release of cholecystokinin (86), a hormone that can augment pancreas size and stimulate pancreatic tumor growth in a mouse model (87).

Finally, both gallstones and cholecystectomy were associated with subsequent risk of ampulla of Vater cancer. The strength of the odds ratios for these associations decreased with increasing time since diagnosis, which may reflect surveillance bias. Only 1 other study evaluated these associations; it found results similar to our own, although in that study only the association with gallstones decreased 5 years after diagnosis (63).

The strengths of our study include the use of a very large data set, which gave us excellent statistical power to investigate less common digestive system cancer subsites. Our study also had high data quality, since SEER has a 95% case ascertainment rate; and use of Medicare data for exposure assessment, instead of personal interviews, enabled us to avoid recall bias. Finally, we assessed gallstones and cholecystectomy before cancer diagnosis and were able to adjust for diabetes, a known risk factor for cancers of the liver (88), pancreas (89), gallbladder (90), and colorectum (91).

Our study also had several limitations. Only gallstones and cholecystectomies reported after Medicare enrollment were identified. Hence, we were not able to identify diagnoses and procedures that took place prior to Medicare enrollment. Although 6.5% of subjects in this study had Medicare claims for gallstones, 10%–20% of Americans will develop gallstones at some time (92). Additionally, the study included only participants aged 66 years or older; thus, our findings may not apply to younger populations. Nonetheless, since Medicare provided the vast majority of medical care to participants in our study population, our study's sensitivity for symptomatic gallstones diagnosed at or after age 66 years was probably good. Additionally, the median age at diagnosis for most examined cancers in the United States is also 66 years or more, with the exception of liver cancer (14). Another limitation was a lack of information on possible confounders which are poorly reflected in Medicare data, especially obesity (92). However, we did not observe associations with esophageal adenocarcinoma, for which obesity is a strong risk factor (93), or with esophageal squamous-cell carcinoma, for which smoking and alcohol consumption are strong risk factors. Adjusting for diabetes also did not change our estimates. Thus, while confounding by other factors is possible, it is unlikely to completely explain our results. Finally, we were not able to evaluate the possible interaction between gallstones and cholecystectomy, since many participants with claims for cholecystectomy had probably had gallstones previously but the diagnosis may not have been captured in their Medicare record.

In conclusion, a history of gallstones and cholecystectomy were associated with an elevated risk of subsequent digestive

tract cancers, including noncardia gastric cancer and small-intestine carcinoid, as well as auxiliary organ cancers, including hepatocellular carcinoma, cholangiocarcinoma, pancreatic cancer, and ampulla of Vater cancer. Both gallstones and cholecystectomy were associated with decreased colorectal cancer risk with increasing distance from the common bile duct. The results of this large US population-based study suggest that changes in bile flow (bile reflux into the stomach or continual excretion into the intestines), local inflammation (increased with gallstones and decreased with cholecystectomy), and changes in hormone levels (cholecystokinin in the pancreas) are important in the etiology of digestive system cancers.

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Author affiliations: Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Leticia Nogueira, Eric Engels, Felipe Castro, Jill Koshiol); Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Neal D. Freedman); and Health Services and Economics Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland (Joan L. Warren).

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