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Increased risk of gallstones after gastrectomy

A longitudinal follow-up study using a national sample cohort in korea

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Abstract

This study sought to evaluate the association between gastrectomy and the occurrence of gallstones using a national sample cohort from Korea.

Data from 2002 to 2013 were collected for individuals ≥20 years of age in the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). We extracted data for patients who had undergone gastrectomy (n = 1998) and a 1:4 matched control group (n = 7992) and then analyzed the occurrence of gallstones. The patients were matched according to age, sex, income, region of residence, hypertension, diabetes mellitus, and history of dyslipidemia. Gastrectomies were identified using operation codes (Q2533-Q2537, Q2594-Q2596, and Q2598). Gallstones were diagnosed if the corresponding *International Classification of Disease-10* code (K80) was reported ≥2 times. Crude (simple) and adjusted hazard ratios (HRs) were analyzed using Cox proportional hazard models, and 95% confidence intervals (CIs) were calculated. Subgroup analyses were performed based on age and sex.

The adjusted HR for gallstones was 1.77 (95% CI = 1.34–2.35, $P < .001$) in the gastrectomy group compared to control. Consistent HRs were found in the analyses of all of the subgroups determined using age and sex.

The occurrence of gallstones was increased in the patients who had undergone gastrectomy compared to their matched control group.

Abbreviations: CIs = confidence intervals, HRs = hazard ratios, HIRA = Health Insurance Review and Assessment, NHIS-NSC = Korean National Health Insurance Service-National Sample Cohort.

Keywords: cholelithiasis, cohort studies, epidemiology., gallstones, gastrectomy, nested case-control studies, stomach

1. Introduction

The risk of gallstone formation after gastrectomy has been reported in many studies .[1,2] Causes include resection of the hepatic branch of the vagus nerve ,[3] nonphysiologic reconstruction,[4] infection of the biliary tract,[5] and altered response and secretion of cholecystokinin.[6,7]

Previously, a few studies analyzed the higher incidence of gallstones after gastrectomy compared to appropriated control groups .[8] Most reported the incidence of gallstones only in gastrectomy patients without control groups .[9–13] The incidence of gallstones after gastrectomy has been reported as 5.2% to 15.2% in Korea,[9–11] 7.4% in Taiwan,[12] and 22.1% in Japan [13], compared with the incidence of gallstones in the general population (3.6% in Korea and 5%–10% in East Asia).[14–17] We found only 1 study that compared the incidence of gallstones between gastrectomy (16.6%) and control (4.4%) groups .[8] However, this study neither matched control groups nor adjusted confounders statistically.

There was need for a study to compare the incidence of gallstones with a control group to be proven scientifically. The purpose of this study is to compare the incidence of gallstones between gastrectomy patients and their matched control group in a large, population-based cohort of Korean patients. To evaluate the age- and sex-specific risks, subgroup analyses were performed.

2. Materials and methods

2.1. Study Population and Data Collection

The ethics committee of Hallym University approved the use of the study data (2014-I148). The requirement for written informed consent was waived by the university's institutional review board.

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The authors report no conflicts of interests.

So Young Kim and Woo Jin Bang have equally contributed in this study.

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This national cohort study relies on data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Korean National Health Insurance Service (NHIS) selects samples directly from a database that includes the entire population to prevent non-sampling errors. Approximately 2% of samples (representing 1 million individuals) were selected from the entire Korean population (50 million individuals). The selected data include age (18 categories), sex (2 categories), and income level (41 categories), with randomized stratified systematic sampling methods involving proportional allocation used to ensure representation of the entire population. The appropriateness of the sample after data selection was verified by a previous study.[18] Details regarding the methods used to perform these procedures are provided by the National Health Insurance Sharing Service.[19] This cohort database included personal information, health insurance claim codes (procedures and prescriptions), diagnostic codes determined using the *International Classification of Disease-10* (ICD-10), death records from the Korean National Statistical Office (that use the Korean Standard Classification of Diseases), socioeconomic data (regarding residence and income), and medical examination data for each participant from 2002 to 2013.

Because a 13-digit resident registration number is used to identify all Korean citizens from birth to death, exact population statistics can be determined using this database. Enrollment in the NHIS is mandatory for all Koreans. All Korean hospitals and clinics use this 13-digit number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one location to another. Moreover, without exception, all medical treatments in Korea can be tracked using the Health Insurance Review & Assessment (HIRA) system. In Korea, submission of a notice of death to an administrative entity is legally required before a funeral can be held. Cause (s) of death and date of death are recorded by medical doctors on a death certificate.

2.2. Participant Selection

Among 1,125,691 patients with 114,369,638 medical claim codes, we included individuals who were treated with gastrectomy. Gastrectomies were identified based on operation codes (total gastrectomy [Q2533–Q2537], subtotal gastrectomy [Q2594–Q2596, and Q2598], n=2037). Gallstones were defined using the *ICD-10* code K80 (cholelithiasis). From the NHIS-NSC, we selected patients who were treated ≥2 times for gallstones (n=21,501).

In the cohort, the participants treated with gastrectomy were matched 1:4 with participants (control subjects) who never underwent gastrectomy between 2002 and 2013. The control group was selected from the mother population (n=1,123,654). The participants were matched based on age, group, sex, income group, region of residence, and medical history (hypertension, diabetes, and/or dyslipidemia). To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order and were then selected from top to bottom. It was assumed that each gastrectomy patient and the matching control participants were receiving any needed medical treatment during concurrent time periods (based on the relevant index date). Therefore, the patients in the control group who died before the index date were excluded. In both the gastrectomy and control groups, the participants with a history of gallstones before the index date were excluded. In the gastrectomy group, 36 participants were excluded. None of the participants were excluded because of lack of matching participants. We excluded the participants younger than 20 years (n=3). Finally, 1:4 matching resulted in the inclusion of 1998 gastrectomy and 7992 control participants (Fig. 1). However, the participants were not matched with respect to ischemic heart disease, cerebral stroke, and history of depression, because strict matching based on these characteristics increased the drop-out rate for subjects owing to a lack of control participants.

2.3. Variables

The following age groups were defined using 5-year intervals: 20–24, 25–29, 30–34 . . . , and 85+ years. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 5 classes (class 1 [lowest income]-class 5 [highest income]). Region of residence was initially divided into 16 areas based on administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The participants' medical histories were evaluated using *ICD-10* codes. To ensure an accurate diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were regarded as present if a participant was treated ≥2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were regarded as present if a participant was treated ≥1 time. Depression was defined based on *ICD-10* codes from F31 (bipolar affective disorder) to F39 (unspecified mood disorder) recorded by a psychiatrist ≥2 times.

2.4. Statistical Analyses

χ^2 tests were used to compare the general characteristics between the gastrectomy and control groups.

Cox-proportional hazard models were used to assess hazard ratios (HRs) for gastrectomy with respect to gallstones. In this analysis, crude (simple) and adjusted (for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression) models were used, and 95% confidence intervals (CIs) were calculated.

For the subgroup analyses, we divided the participants by age (<60 and ≥60 years old) and sex (men and women).

Two-tailed analyses were conducted, and *P* values <0.05 were regarded as indicative of significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

The mean follow-up was 89.0 months (standard deviation [SD]= 37.4) in the gastrectomy group and 90.1 months (SD=36.7) in the control group. The time interval between the index date and the occurrence of gallstones was 43.3 months (SD=32.7) in the gastrectomy group and 52.9 months (SD=32.3) in the control group. The rate of gallstones was higher in the gastrectomy group (3.5% [70/1998]) than in the control group (2.0% [159/7992], $P < .001$, Table 1). The 2 groups of participants were identical with respect to the general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories) owing to matching ($P=1.000$). The rates of cerebral stroke were different between the gastrectomy and control groups ($P < .05$).

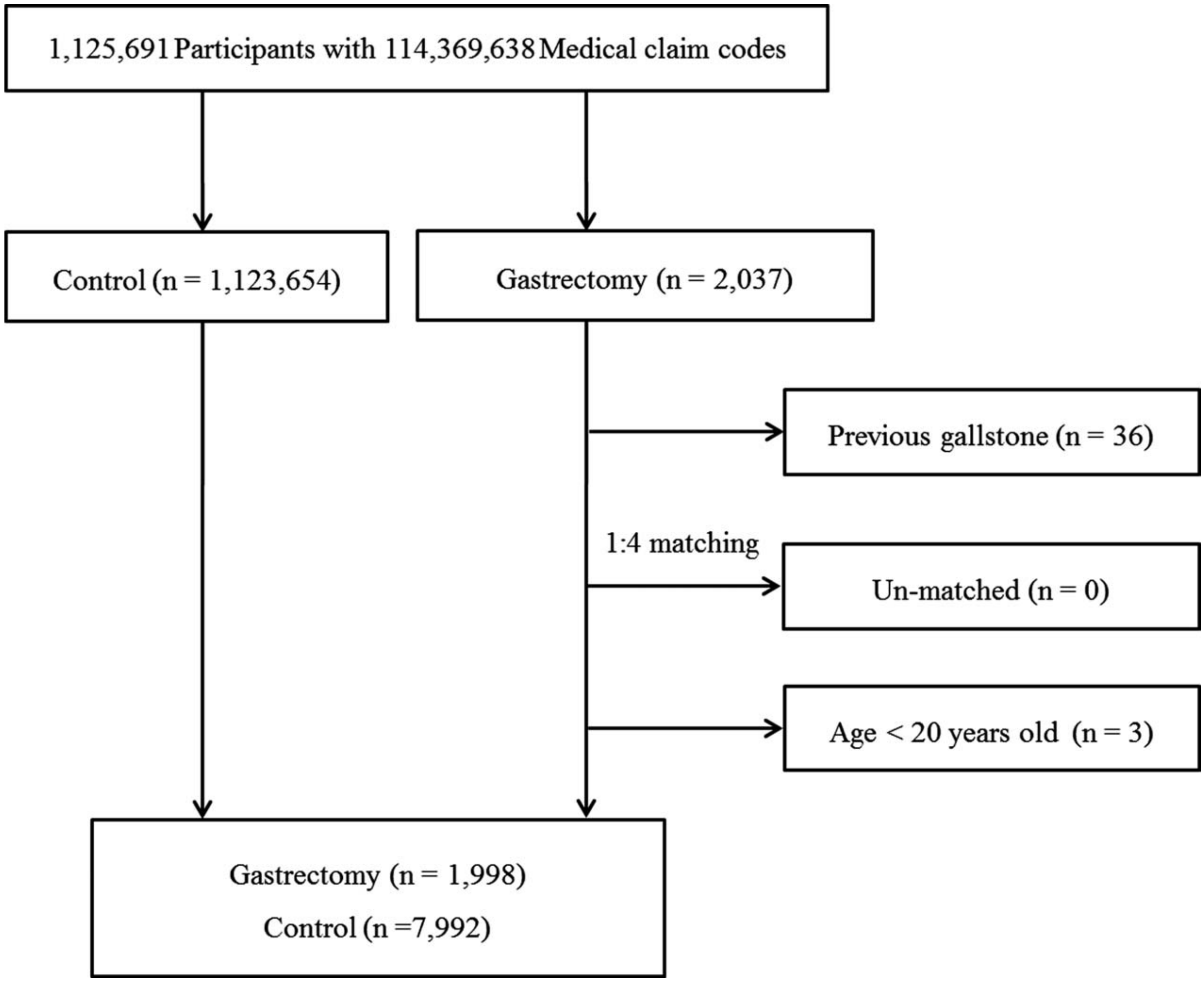

Figure 1. A schematic illustration of the participant selection process used in the present study. Among a total of 1,125,691 individuals, 1,998 gastrectomy patients were matched with 7992 control participants based on age, group, sex, income group, region of residence, and medical history.

Crude and adjusted HRs for gallstones were 1.78 (95% CI=1.35–2.36) and 1.77 (95% CI=1.34–2.35) in the gastrectomy group, respectively ($P < .001$ for both comparisons, Table 2).

In the subgroup analyses according to age and sex, crude and adjusted HRs for gallstones were higher in the gastrectomy group than those in the control group for all age groups and sexes. The adjusted HRs were 2.22 (95% CI=1.47–3.36) in <60-year-old age group, 1.49 (95% CI=1.01–2.19) in ≥ 60-year-old age group, 1.70 (95% CI=1.22–2.36) in men, and 2.02 (95% CI=1.18–3.47) in women ($P < .05$ for each comparison, Table 3).

4. Discussion

The present study demonstrated that gastrectomy increased the risk of gallstones compared to matched control (adjusted HR=1.77, 95% CI=1.34–2.35). We could not compare the HR because of lack of results in previous studies,[9–13] which only described the incidence of gallstones in gastrectomy patients and the known incidence of gallstone in general population. We found these associations in all subgroups (<60 years' old, ≥60 years' old, men, and women).

The incidence of gallstones was 3.5% in the gastrectomy group and 2.0% in the control group. The incidence of gallstones was lower than previous studies.[9–13] This study only included the gallstone participants who visited the hospital because it used medical claim codes. This means that asymptomatic gallstones were not detected in this study. Moreover, up to 80% of gallstones did not provoke complications such as cholecystitis, cholangitis, or pancreatitis.[20] Therefore, the detected gallstone rate was low in this study. However, we could conclude that at least the detected or symptomatic gallstone rate was higher in the gastrectomy group than in the control.

The higher incidence of gallstones in the gastrectomy group might be a result of detection bias, in that the gastrectomy participants might have had a higher likelihood of having computed tomography or ultrasonography. Therefore, we analyzed the incidence of gallstones confined to 6 months after gastrectomy (S1 table, http://links.lww.com/MD/D24). In this analysis, the risk of gallstones was still higher in the gastrectomy group (adjusted HR=1.63, 95% CI=1.21–2.20, P=0.001). In subgroup analyses according to age and sex, younger and women subgroups demonstrated higher adjusted HRs in the present study. These higher risks of gallstones in gastrectomy patients among women might be related with high prevalence of gallstone in this population. Women were suggested to be at a higher risk of developing gallstones as the levels of reproductive hormones were

Table 1

General characteristics of participants.

Characteristics	Total participants		
	Gastrectomy, n (%)	Control group, n (%)	*P*
Age, y			1.000
20–24	4 (0.2)	16 (0.2)	
25–29	12 (0.6)	48 (0.6)	
30–34	27 (1.4)	108 (1.4)	
35–39	73 (3.7)	292 (3.7)	
40–44	149 (7.5)	596 (7.5)	
45–49	174 (8.7)	696 (8.7)	
50–54	218 (10.9)	872 (10.9)	
55–59	250 (12.5)	1000 (12.5)	
60–64	338 (16.9)	1352 (16.9)	
65–69	337 (16.9)	1348 (16.9)	
70–74	256 (12.8)	1024 (12.8)	
75–79	122 (6.1)	488 (6.1)	
80–84	30 (1.5)	120 (1.5)	
85+	8 (0.4)	32 (0.4)	
Sex			1.000
Male	1351 (67.6)	5404 (67.6)	
Female	647 (32.4)	2588 (32.4)	
Income			1.000
1 (Lowest)	278 (13.9)	1112 (13.9)	
2	270 (13.5)	1080 (13.5)	
3	333 (16.7)	1332 (16.7)	
4	444 (22.2)	1776 (22.2)	
5 (Highest)	673 (33.7)	2692 (33.7)	
Region of residence			1.000
Urban	915 (45.8)	3660 (45.8)	
Rural	1083 (54.2)	4332 (54.2)	
Hypertension			1.000
Yes	796 (39.8)	3184 (39.8)	
No	1202 (60.2)	4808 (60.2)	
Diabetes			1.000
Yes	576 (28.8)	2304 (28.8)	
No	1422 (71.2)	5688 (71.2)	
Dyslipidemia			1.000
Yes	413 (20.7)	1652 (20.7)	
No	1585 (79.3)	6340 (79.3)	
Ischemic heart disease			.896
Yes	153 (7.7)	619 (7.7)	
No	1845 (92.3)	7373 (92.3)	
Cerebral stroke			0.029*
Yes	257 (12.9)	1181 (14.8)	
No	1741 (87.1)	6811 (85.2)	
Depression			0.083
Yes	208 (10.4)	731 (9.1)	
No	1790 (89.6)	7261 (90.9)	
Gallstone			<0.001*
Yes	70 (3.5)	159 (2.0)	
No	1928 (96.5)	7833 (98.0)	

* χ^2 test. Significance at $P<.05$.

Table 2

Crude and adjusted hazard ratios (95% confidence interval) of gastrectomy for gallstone.

Characteristics	Gallstone			
	Crude	*P*	Adjusted†	*P*
Gastrectomy	1.78 (1.35–2.36)	<.001*	1.77 (1.34–2.35)	<.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P<.05$.
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, depression histories.

Table 3

Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval) of gastrectomy for gallstone according to age and sex.

Characteristics	Gallstone			
	Crude	*P*	Adjusted*	*P*
Age <60 y (n=4535)				
Gastrectomy	2.22 (1.47–3.36)	<.001†	2.22 (1.47–3.36)	<.001†
Control	1.00		1.00	
Age ≥60 y (n=5455)				
Gastrectomy	1.49 (1.01–2.19)	.045†	1.49 (1.01–2.19)	.046†
Control	1.00		1.00	
Men (n=6755)				
Gastrectomy	1.69 (1.21–2.35)	.002†	1.70 (1.22–2.36)	.002†
Control	1.00		1.00	
Women (n=3235)				
Gastrectomy	2.07 (1.21–3.55)	.008†	2.02 (1.18–3.47)	.011†
Control	1.00		1.00	

* Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, depression histories.
† Cox-proportional hazard regression model, Significance at $P < .05$.

found to be inversely related with the incidence of gallstone.[21] Thus, the effects of reduced levels of reproductive hormones might be more prominent in women. In young population, high impact of fat and related diseases could increase the risk of gallstone after gastrectomy patients compared to older population. High fat and fatty liver disease in young and middle age populations was related to the high risk of gallstone in a previous study.[22]

The strength of this study is the use of a large, representative, nationwide population sample, which is consistent with our previous studies.[23–25] As stated above, we randomly selected controls with 1:4 matching for age, sex, income, region of residence, and medical histories. This design made it possible to compare the incidence of gallstones in gastrectomy participants with an appropriate control group. The rate of stroke was higher in gastrectomy group than control group in this study. However, a few previous studies reported the improvement of cardiovascular risk profiles and stroke after gastrectomy .[26,27] However, these studies compared between preoperative and postoperative status. Thus, the healthy lifestyle after gastrectomy could influence lower cardiovascular risk profiles in these patients. In addition, this study matched control group for a number of cardiovascular risk factors including hypertension, diabetes, and dyslipidemia. Furthermore, an adjusted regression model was used to minimize the confounders. Because of the large number of participants, we could maintain statistical power even when subgrouping the participants, thus allowing subgroup analyses.

This study has several limitations. As stated above, we could not find gallstone participants without symptoms to include in this study. Despite the large number of participants, we did not analyze the risk of gallstones according to types of surgeries. The statistical power was not enough to stratify according to types of surgeries. We could not analyze possible confounding factors between gastrectomy and gallstone, such as smoking, obesity, weight loss, and dietary habits. Finally, our study could not confirm a pathophysiological mechanism between gastrectomy and gallstones, as we calculated only HRs. Additionally, we did not describe the known pathophysiology because it was well-described in other studies.[3–7,9–13]

5. Conclusion

The occurrence of gallstones was increased in the participants who underwent gastrectomy compared with the matched control participants.

Author contributions

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