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Is gallbladder cancer decreasing in view of increasing laparoscopic cholecystectomy?

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ABSTRACT

Background. Gallstone disease affects over 20 million people in the U.S. and is a major risk factor for gallbladder cancer (GBC). In 1988, a less invasive, low-cost procedure, laparoscopic cholecystectomy (LC), was introduced and became the standard of care for management of gallstones. **Methods.** GBC incidence (1973-2007) and mortality rates (1969-2006) were calculated using SEER Program data. LC rates (1993-2008) were obtained from NAMCS, NHAMCS, and HCUP. Annual percent change was estimated by gender, age, and race, and the statistical significance was assessed at $p < 0.05$. Correlation analysis was performed on GBC and LC trends. **Results.** Since the early 1970s, GBC incidence and mortality rate have declined. Women and older age groups continue to have the highest risk for GBC, despite having greater declines. Incidence significantly decreased among whites, but did not among blacks. The number of inpatient LC procedures increased by 15% between 1994 and 2008; however, inpatient and outpatient LC rates remained stable. LC rate was not significantly correlated with either GBC incidence or mortality. **Conclusions.** The decline in incidence and mortality of GBC began decades before the introduction of LC and apparently has stabilized in the past decade. No temporal relationship existed between LC rate and the incidence and mortality rates of GBC. Our study suggests that prevention of a rare tumor may be extremely difficult if the surgical removal of a risk factor is involved.

Key words. Gallbladder cancer. Laparoscopic. Cholecystectomy. Trends. Epidemiology.

INTRODUCTION

Gallbladder cancer (GBC) is the most common cancer of the biliary tract worldwide.[1] It is characterized by wide geographic variation with distinctive pockets of high incidence in Central and South America, Central and Eastern Europe, South Asia, and Japan.[2,3] The highest incidence rate worldwide is among women in Delhi, India (21.5 per 100,000).[4] In Western Europe and the U.S., however, it is an uncommon cancer (1 per 100,000), except among American Indians and Hispanics (about 8 per 100,000).[2-8]

Despite the rarity of the disease, it is an aggressive malignancy. Prognosis is poor on account of nonspecific symptoms at presentation and late-stage diagnoses: 75% of patients are diagnosed with the disease when it is beyond the limits of resection.[1] Overall median survival for advanced stage GBC is 2-5 months.[7] It is also one of the few cancers found predominantly among women, except in Japan and Korea where the female to male incidence ratio is approximately one.[1,2]

Cholelithiasis, or gallstone disease, is the major risk factor for gallbladder cancer and affects an estimated 20.5 million people ages 20-74 years in the U.S.[9] Though 1-3% of people with cholelithiasis develop gallbladder cancer in the U.S., it is present in 60-90% of gallbladder cancer cases around the world.[2] Additional risk factors are those associated with gallstones: age, diet, socioeconomic status, obesity, and genetics.[1,2] In the absence of gallstones, having a congenitally abnormal choledochopancreatic junction has been associated with GBC.[10]

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Management of gallstones entails performing a cholecystectomy. Open cholecystectomy (OC) refers to conventional major abdominal surgery to remove the gallbladder. On account of the risks and costs of major surgery, cholecystectomy did not become the standard of care for the treatment of gallstones until after the introduction of laparoscopic cholecystectomy (LC) in 1988. LC is as effective, less invasive, and has a shorter recovery time compared with OC. For these reasons, it is now the most frequent of all intra-abdominal operations with an estimated 700,000 procedures performed annually in the U.S.[2] Among persons with cholelithiasis, about one-third has undergone a cholecystectomy.[6]

Recent studies in Europe have described declining rates of incidence and mortality in gallbladder cancer, whereas Chile and Japan have seen increases.[2-4,11,12] Some studies have hypothesized that increased utilization of LC may play a role in the declining mortality and incidence rates.[11,12] However, the use of elective cholecystectomy as a secondary prevention of gallbladder cancer is controversial.[3,13] The trends in GBC and LC have not recently been characterized in the U.S. This study will describe trends in GBC incidence and mortality rates and LC rates. Additionally, we will examine the relationship between GBC and LC rates.

METHODS

Data sources

Data on GBC incidence and mortality were obtained from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program. The original 9 registries cover approximately 12% of the U.S. population.[15]

LC may be performed in either an inpatient or outpatient (or ambulatory) setting. Discharge data from the Nationwide Inpatient Sample (NIS) were obtained to describe trends in LCs performed in an inpatient setting.[17] NIS is a multistate, all-payer inpatient database created as a part of the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (AHRQ). It is a 20% sample of U.S. community hospitals and allows for national estimates of hospital discharges.[16,18]

Datasets from the National Ambulatory Care Survey (NAMCS) and the National Hospital Ambulatory Care Survey (NHAMCS) were combined and used to obtain data on LCs performed in an ambulatory setting.[19,20] NAMCS/NHAMCS, administered by the National Center for Health Statistics at the Center for Disease Control (CDC/NCHS), collects data on the utilization and provision of ambulatory services. They are national probability sample surveys of visits to non-federal, office-based physicians (NAMCS) and to the emergency and outpatient departments of non-institutional general and short-stay hospitals (NHAMCS).[21]

Measurements and statistical analyses

Annual incidence rates were calculated for GBC from 1973 to 2007; mortality rates were calculated from 1969 to 2006. Calculations for LC rates were performed separately for inpatient and outpatient procedures. Data on inpatient LC procedures were available for alternating years between 1994 and 2008, and on outpatient procedures for all years between 1993 and 2007. We reported overall rates for LC and GBC incidence and mortality and stratified by gender, race and age where possible. Analysis by race compared only whites and blacks due to limitations on race coding. Rates were expressed per 100,000 and age-adjusted to the standard 2000 U.S. population.

Analyses of LC data were performed using survey analysis methods to produce national estimates (SAS v9.1.3, SAS Institute, Inc., Cary, North Carolina). We queried all-listed procedure codes for LC, identified by the code '51.23' using the Clinical Modification of the International Classification of Diseases, 9th Revision (ICD-9-CM). Procedures in which the patient is admitted to the hospital for overnight stay post-surgery are considered *inpatient* LC. Procedures in which the patient is released same-day post-surgery, usually performed in ambulatory care centers or hospital outpatient departments, are referred to as *outpatient,* or *ambulatory,* LC. Estimates were considered reliable if there were at least 30 raw cases and the relative standard of error was less than 30%. Population rates of LC were calculated using national estimates and U.S. Census data.[22]

Trends were examined by linear regression analysis using annual percent changes (APC), the average decrease (or increase) in rates over a time period. The APC was calculated by fitting a weighted least squares regression line to the natural log of the rates and taking the slope of the regression line (SEER*Stat v6.6.2). We performed Pearson's correlation analysis to examine the relationship between trends in LC and the following year GBC incidence and mortality rates (SAS v9.1.3). The Student's t-test was used to test the coefficients for significance at the $\alpha = 0.5$ level.

RESULTS

Gallbladder cancer incidence

Between 1973 and 2007, the overall, age-adjusted incidence rate of GBC significantly decreased by 1.86% per year from 1.99 to 1.14 per 100,000 persons (Figure 1, Table 1). When stratified by 10-year age groups, annual incidence rates were higher with increasing age and the greatest declines in rates were seen among older age groups. Incidence among those ages 80 and older decreased by 2.34% annually from 16.9 per 100,000 to 11.2, whereas among those ages 50-59 years old it decreased by 1.22% annually from 1.39 to 1.02. No significant changes in incidence rates occurred among those ages 40 to 49. Statistics could not be calculated for those under 40 because of the paucity of cases in the age groups.

Among men, incidence decreased from 1.29 per 100,000 to 0.80, or an annual percent decrease of 1.40%. While rates among women also decreased, they remained almost twice those of men: 2.50 in 1973 and 1.41 in 2007. Annual incidence rates did not differ significantly between whites and blacks; however, trends among whites and blacks differed significantly. Among whites, incidence rates decreased by 2.10% per year; over the same period, rates were stable among blacks.

Gallbladder cancer mortality

Since 1969, the mortality rate for GBC significantly declined from 1.50 per 100,000 to 0.67 in 2006, an annual decrease of 2.69% (Figure 1, Table 2). Mortality rates among all age groups ≥ 40 years declined by about half or more over four decades, but mortality remained higher among older age groups. Mortality rates declined among both men (1.06 to 0.45) and women (2.33 to 0.81), but by more among women: a decrease of 2.25% in men compared with 2.82% in women. Significant differences in trends were evident by race. Rates declined by 66% among whites from 1.85 to 0.63, whereas the decline among blacks was modest from 1.07 to 0.83. Annual mortality rates were significantly higher in whites than in blacks in the 1970s. During the 1980s and 1990s, rates did not differ significantly between the two groups; however, in the last decade, rates in blacks have remained significantly higher than those in whites (Figure 2).

Table 1. Trends in age-adjusted gallbladder cancer incidence rate.

	1973		2007		APC (95% CI)
	Rate	95% CI	Rate	95% CI	
• Overall	1.99	1.75-2.27	1.14	1.02-1.28	-1.86* (-2.10 to -1.63)
• Sex					
Male	1.29	0.98-1.66	0.80	0.64-0.98	-1.40* (-1.84 to -0.96)
Female	2.50	2.15-2.90	1.41	1.23-1.61	-1.95* (-2.20 to -1.71)
• Race					
White	1.97	1.71-2.25	1.07	0.94-1.22	-2.10* (-2.33 to -1.87)
Black	1.80	0.88-3.33	1.42	0.98-1.98	0.32 (-0.46 to 1.12)
• Age					
80+	16.87	12.56-22.15	11.19	9.22-13.45	-2.34* (-2.71 to -1.97)
70-79	13.33	10.74-16.36	6.34	5.08-7.81	-2.04* (-2.43 to -1.65)
60-69	5.97	4.65-7.55	2.66	2.02-3.43	-1.72* (-2.17 to -1.28)
50-59	1.39	0.90-2.05	1.02	0.73-1.40	-1.22* (-1.75 to -0.68)
40-49	0.38	0.15-0.78	0.45	0.27-0.69	-0.12 (-1.05 to 0.82)
30-39	0	0-0.20	0.10	0.03-0.26	--
20-29	0	0-0.14	0.05	0.01-0.18	--
< 20	0	0-0.60	0	0-0.05	--

Rates are age-adjusted (per 100,000). APC: Annual percent change in rate. CI: Confidence interval. --: Indicates could not be calculated. *Indicates statistical significance $p < 0.05$.

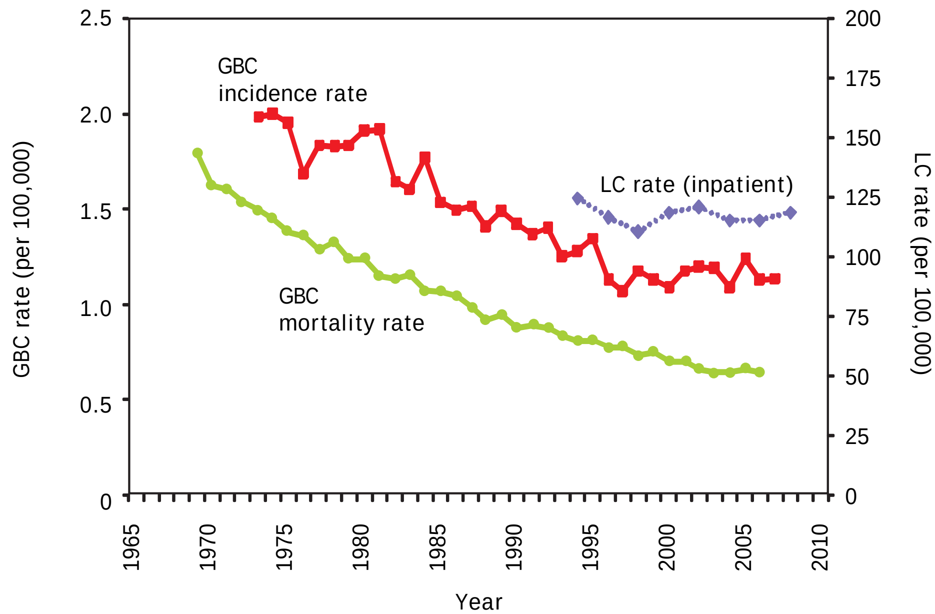

Figure 1. Secular trends in age-adjusted gallbladder cancer incidence rate (1973-2007) and mortality rate (1969-2007), as well as inpatient laparoscopic cholecystectomy (1994-2008).

Table 2. Trends in age-adjusted gallbladder cancer mortality rate.

	1969		2006		APC (95% CI)
	Rate	95% CI	Rate	95% CI	
• Overall	1.79	1.72-1.86	0.65	0.62-0.68	-2.69* (-2.78 to -2.60)
• Sex					
Male	1.06	0.98-1.15	0.45	0.41-0.49	-2.25* (-2.36 to -2.13)
Female	2.33	2.23-2.44	0.81	0.76-0.85	-2.82* (-2.94 to -2.70)
• Race					
White	1.85	1.77-1.92	0.63	0.60-0.66	-2.89* (-2.98 to -2.80)
Black	1.07	0.88-1.28	0.83	0.72-0.94	-0.46* (-0.70 to -0.21)
• Age					
80+	16.80	15.46-18.22	6.03	5.58-6.51	-2.81* (-2.97 to -2.65)
70-79	11.15	10.47-11.86	3.65	3.36-3.96	-3.04* (-3.19 to -2.88)
60-69	4.76	4.42-5.12	1.70	1.54-1.88	-2.56* (-2.77 to -2.35)
50-59	1.52	1.36-1.70	0.64	0.57-0.73	-2.12* (-2.34 to -1.90)
40-49	0.34	0.27-0.42	0.19	0.15-0.23	-1.33* (-1.70 to -0.95)
30-39	0.04	0.02-0.07	0.04	0.02-0.06	—
20-29	—	—	—	—	—
<20	0	—	0	—	—

Rates are age-adjusted (per 100,000). APC: Annual percent change in rate. CI: Confidence interval. --: Indicates could not be calculated. *Indicates statistical significance $p < 0.05$.

Laparoscopic cholecystectomy

Between 1994 and 2008, the number of inpatient LC procedures increased from 327,387 to 369,883, but the rate of inpatient LC procedures did not significantly change from 125.8 to 121.6 per 100,000 persons (Table 3). The number of men having inpatient LC performed increased by 41% between 1994 and 2008. Rates among men have significantly increased by 1.46% annually, but have remained sta-

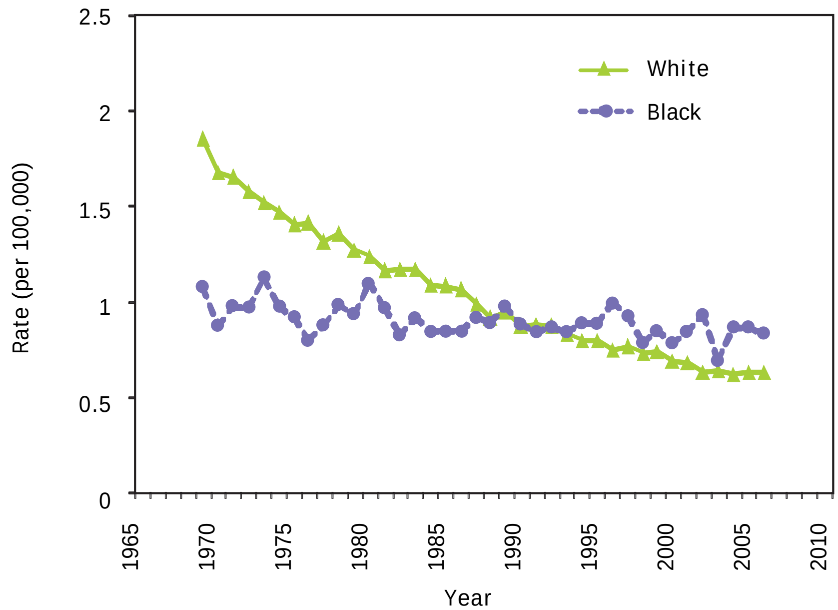

Figure 2. Trends in age-adjusted gallbladder cancer mortality rates, by race, 1969-2006.

Table 3. Trends in inpatient laparoscopic cholecystectomy frequency and rate.

	1994		2008		APC (95% CI)
	Frequency	Rate	Frequency	Rate	
• Overall	323.0 ± 17.6	124.9 ± 6.7	369.9 ± 21.7	118.8 ± 7.1	-0.14 (-0.9 to 0.6)
• Sex					
Male	84.9 + 2.4	66.0 ± 3.7	119.8 ± 3.7	77.7 ± 4.7	1.46* (0.7 to 2.2)
Female	238.4 ± 6.8	177.2 ± 9.9	248.1 ± 7.5	165.3 ± 9.8	-0.41 (-1.2 to 0.4)
• Age					
80+	19.9 ± 1.4	250.3 ± 17.3	33.3 ± 2.1	295.1 ± 19.0	0.77 (-0.1 to 1.7)
70-79	48.0 ± 2.9	312.1 ± 19.1	46.7 ± 3.0	288.7 ± 18.4	-0.62* (-1.2 to -0.1)
60-69	53.4 ± 3.2	264.7 ± 16.0	52.5 ± 3.4	198.6 ± 12.8	-1.81* (-2.5 to -1.2)
50-59	50.5 ± 3.3	207.0 ± 13.4	58.6 ± 3.7	146.7 ± 9.4	-2.33* (-3.2 to -1.5)
40-49	53.8 ± 3.5	147.4 ± 9.6	59.6 ± 4.1	134.8 ± 9.2	-0.23 (-1.6 to 1.1)
30-39	52.8 ± 3.5	118.1 ± 7.7	54.2 ± 3.7	134.4 ± 9.2	1.57* (0.3 to 2.9)
20-29	38.2 ± 2.4	99.4 ± 6.1	50.9 ± 3.5	119.0 ± 8.1	1.65* (0.7 to 2.6)
< 20	6.7 ± 0.6	9.2 ± 0.8	14.1 ± 1.5	17.0 ± 1.7	4.26* (3.5 to 5.0)

Frequency (per 1,000). Rates are age-adjusted (per 100,000). APC: Annual percent change in rate. CI: Confidence interval. --: Indicates could not be calculated. *Indicates statistical significance p < 0.05.

ble for women. The procedure is less frequently performed in youngest (< 20 years) and oldest age groups (80+ years). Rates, however, are higher with increasing age. During the past 15 years, rates have significantly declined among those 50-79 years old, but increased among younger age groups (< 40 years). Reliable estimates of inpatient LC by race were not available.

Outpatient LC procedures almost doubled between 1993 and 2004 from 247,326 to 490,878. However, estimates were only reliable for the years 1993, 1994, 2002, and 2004. Rates appear to have increased from 95.0 per 100,000 to 167.6; however, this increase was not statistically significant. Rates were not age-adjusted and estimates could not be reported by sex or age group due to the small number of raw records.

Table 4. Correlation coefficients for inpatient laparoscopic cholecystectomy rate *vs.* following-year gallbladder cancer incidence and mortality rates.

r	GBC			
LCR	Incidence	p-value	Mortality	p-value
• Overall				
Inpatient	0.704	0.08	0.145	0.78
• Sex				
Male	-0.163	0.73	-0.676	0.14
Female	0.408	0.36	0.101	0.85
• Age				
80+	-0.215	0.64	-0.813*	0.049
70-79	0.107	0.82	0.426	0.40
60-69	0.704	0.08	0.765	0.08
50-59	0.262	0.57	0.611	0.20
40-49	-0.509	0.24	0.151	0.78
30-39	0.618	0.14	-0.703	0.12
20-29	0.651	0.11	—	—
<20	—	—	—	—

r: Pearson's correlation coefficient of LCR *vs.* GBC Inc/Mort in the following year. —: Indicates could not be calculated. *Indicates statistical significance $p < 0.05$.

Relationship between gallbladder cancer and laparoscopic cholecystectomy

Correlation analysis of inpatient LC rate *vs.* GBC incidence or mortality rates showed weak or no significant correlation (Table 4). Inpatient LC rate in a given year and GBC incidence rate in the following year were positively correlated but not significant ($r = 0.704$, $p = 0.08$). There was no correlation between inpatient LC rate and following year GBC mortality rate. The relationship between inpatient LC and GBC incidence and mortality was negatively correlated for men and positively for women. Age-specific correlations were positive, except among those ages 40-49 years, 30-39 years, and 80+ years. The relationship between inpatient LC rate and GBC mortality among those 80+ years was negatively correlated and significant ($r = -0.813$, $p = 0.049$).

Limitations of outpatient LC data did not allow for correlation analysis.

DISCUSSION

The prevailing theory behind declining rates of gallbladder cancer incidence and mortality suggests that increasing laparoscopic cholecystectomy rates may reduce the main risk factor for GBC, namely cholelithiasis.[11,12,14] Our study showed no such inverse relationship between GBC incidence and mortality and LC rates in the U.S. While GBC incidence and mortality rates have declined significantly over the past four decades, this decreasing trend preceded the introduction of the laparoscopic procedure and rates appear to have stabilized since then (Figure 1). The reason for this is not apparent.

Before the introduction of LC, open cholecystectomy (OC) had typically been performed in patients with symptomatic gallstone disease, as many as 536,000 were estimated in 1987.[13] Improvements in technology, such as ultrasonography, have helped to detect and diagnosis gallstone disease and to identify those at greatest risk for GBC as candidates for cholecystectomy.[23] Diehl, *et al.*, showed a significant negative correlation between OC rates and GBC mortality in the U.S., the U.K., and Sweden from 1967 to 1978.[14] Thus, OCs may explain the early decreasing trends in GBC incidence and mortality. Given that an estimated 700,000 LCs are performed annually,[2] we would expect rates to further decrease, not stabilize.

In the absence of a correlation, one could infer that LC has had no direct impact on GBC incidence and mortality. However, it is also possible that effects are masked by, but not limited to, increasing incidental cases of GBC, longer lag-time for effects, and/or lowered clinical indicators for surgery, as well as changes in the prevalence of unknown risk factors. Incidental discovery of GBC after cholecystectomy is one of three ways in which GBC manifests and is reported to occur in 1-3% of LCs.[24] With the frequency of cholecystectomies increasing, incidental discovery of GBC may also be expected to rise. Thus, cases prevented by elective LC could be somewhat balanced by incidental identification of cases that may not otherwise have been detected.

Average age for GBC diagnosis is about 71 years in women and 72.2 years in men.[10] However, symptoms for gallstones may present many years earlier: 2% of men and 7% of women ages 20 to 29 years have gallbladder disease.[23] Due to the advantages of an endoscopic procedure, those who are symptomatic, and in some cases asymptomatic, may elect to have a cholecystectomy and avoid long-term complications of gallbladder disease, such as cholecystitis or GBC. The frequency of LCs is highest among those ages 30-69 years. In the population who has had an OC or LC, a diagnosis of GBC may not have occurred for 10 to 40 years. Some authors conservatively proposed a lag-time of 15-20 years.[12] Our correlation analysis looked at the effect of LC rate on the following-year GBC incidence or mortality rate, but another decade or more may need to pass before an effect may be observed.

Whereas OC was reserved for those with mild to severe symptoms of cholelithiasis, LC has been performed in individuals both symptomatic and asymptomatic for gallstones.[3,25] A lower clinical threshold for surgery could capture a wider at-risk pool and prevent more cases, or it may add to the healthcare burden increasing the number of unnecessary surgeries. If the latter is true, the effects of LC on GBC may become diluted because the additional surgeries are not removing those with the highest risk for GBC.

Another key finding was that the risk of GBC has shifted from whites to blacks. Though the lowest rates were once found among blacks, incidence and mortality rates among blacks have exceeded those of whites since the mid-1990s (Figure 2). This may in part be due to racial differences in the risk of gallbladder disease. Compared with non-Hispanic whites, non-Hispanic black men and women had a lower prevalence of gallstones disease, even after adjustment for other potential risk factors.[9] This higher risk of GBC and, paradoxically, lower prevalence of gallstones suggest possible etiologic differences in GBC by race.

No study has been conducted recently to examine the relationship between national trends in LC and GBC. Because we were interested in a rare disease, using population-based surveys improved the study's power to detect small but significant changes in GBC incidence and mortality that may not be possible at the state or local level. To our knowledge, we are also the first to report LC rates for both inpatient and outpatient procedures.

True incidence and mortality is the frequency of cases over the population at-risk. We used the U.S. mid-year population as the denominator for GBC and LC rates, but the at-risk population is, in fact, the number of people in the U.S. with gallbladders. Estimating the at-risk population is a challenging task, but this calculation would have facilitated a more accurate assessment of GBC and LC trends in the population. The proportion who has had a cholecystectomy represents < 3% of the population,[27] so it is unlikely to have significantly biased rate estimates.

This study also has several limitations. Though GBC is uncommon, using the SEER program, we were able to describe national rates and detect significant trends in GBC incidence and mortality. However, when analyzing subpopulations, we reduce that power. This is evident when analyzing GBC by race. Among blacks, GBC mortality declined slightly but significantly (Figure 2); trends in GBC incidence showed greater variability and no significant change (Table 1). GBC mortality decreased in blacks; thus, there may have been insufficient power to demonstrate a decline in GBC incidence among blacks. Additionally, for these reasons, as well as incomplete race/ethnicity data in SEER, we were unable to analyze trends in GBC among Hispanics.

Discharge data has typically been used to measure cholecystectomy rates, but it neglects the substantial contribution of procedures performed in the ambulatory care setting. Few national surveys have been conducted to study ambulatory surgical care; therefore, accurate and available data are limited. We used the NAMCS and NHAMCS, instead of the National Survey of Ambulatory Surgery (NSAS), because annual data were available for the former but not the latter. The NAMCS/NHAMCS sample included office-based physicians and hospital outpatient departments, but it did not include free-standing ambulatory surgical centers (ASCs), which had been captured by the NSAS. In Florida, < 1% of outpatient LCs were performed in ASCs, but patients at ASCs tended to be white, younger and have private insurance,[28] but it is unknown whether this can be generalized or varies across the U.S. Exclusion of ASCs in the sample may underestimate and skew rates. Selection bias may have also resulted from low participation rates: response rates for the NAMCS varied between 55 and 75%.[26]

Of the 15 years of NAMCS/NHAMCS data we

analyzed, national estimates were reliable for only four of those years. Those estimates were based on a small number of raw records, which prevented us from performing sex- and age-specific analyses. Outpatient LC estimates must be cautiously interpreted because of the low precision of the estimates and the few data points available for trend analysis.

In summary, the increased frequency of laparoscopic cholecystectomies does not seem to explain the decline in gallbladder cancer incidence or mortality. We found no clear temporal relationship between rate of LC performed and the following-year incidence and mortality rates of GBC between 1993 and 2008. The use of prophylactic mastectomy and hysterectomy in high-risk individuals has been associated with reduced incidence in breast cancer and uterine cancer, respectively.[29-31] Likewise, treatment of gallstones by LC represents a potential preventive approach for GBC. However, for such an uncommon cancer, it may be necessary to perform many cholecystectomies in order to significantly reduce the risk of GBC. Our study suggests that it may be difficult to demonstrate significant effects from a preventive measure for a rare tumor.

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CONFLICTS OF INTEREST DECLARED

None.

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