Gallbladder Cancer Incidence and Mortality, United States 1999–2011

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Abstract

Background: Gallbladder cancer is a rare cancer with unusual distribution, and few population-based estimates for the United States have been published.

Methods: Using population-based cancer incidence and mortality data, we examined U.S. gallbladder cancer incidence and death rates for 2007–2011 and trends for 1999–2011.

Results: During 2007 to 2011, approximately 3,700 persons were diagnosed with primary gallbladder cancer (rate = 1.13 cases per 100,000) and 2,000 died from the disease (rate = 0.62 deaths per 100,000) each year in the United States. Two thirds of gallbladder cancer cases and deaths occurred among women. Gallbladder cancer incidence and death rates were three times higher among American Indian and Alaska Native persons than non-Hispanic white persons. By state, gallbladder cancer incidence and death rates ranged by about 2-fold. During 1999 to 2011, gallbladder cancer incidence rates decreased among women but remained level among men; death rates declined among women but stabilized among men after declining from 1999 to 2006. Gallbladder cancer incidence rates increased in some subgroups, notably among black persons, those aged <45 years, and for endocrine tumors.

Conclusions: Data from U.S. population-based cancer registries confirm that gallbladder cancer incidence and death rates are higher among women than men, highest among American Indian and Alaska Native persons, and differ by region. While overall incidence and death rates decreased during 1999 to 2011, incidence rates increased among some small subgroups.

Impact: Surveillance of gallbladder cancer incidence and mortality, particularly to monitor increases in subgroups, may provide clues to etiology and stimulate further research. *Cancer Epidemiol Biomarkers Prev; 24(9); 1319–26. ©2015 AACR.*

Introduction

Gallbladder cancer is a rare, lethal cancer with unusual distribution. It is often diagnosed at a late stage and has poor prognosis (1). It is one of the few cancers that is more common among women than men; worldwide, women typically experience gallbladder cancer incidence two to three times the rate among men, although this ratio ranges from 1 in parts of China to more than 5 in Spain (1). Gallbladder cancer incidence is characterized by marked geographic variation; worldwide, there are fewer than 2 cases per 100,000 persons with higher rates (>10) observed in parts of Poland, India, Pakistan, Bolivia, and Chile, especially among indigenous populations (2, 3). It is one of the few cancers in the United States with low incidence among black persons but high incidence among American Indian and Alaska Native (AI/AN) persons and Hispanic persons (4–7). Few studies using population-based data in the United States, particularly state-specific data, have been published.

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Population-based data are available on cancer incidence from the Centers for Disease Control and Prevention (CDC) National Program for Cancer Registries (NPCR) and the National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER) and on cancer mortality from CDC National Center for Health Statistics (NCHS) National Vital Statistics System (NVSS; ref. 8). Using these data, we examine how patterns of gallbladder cancer incidence and mortality differ by demographic and tumor characteristics.

Materials and Methods

Data about cancer incidence and mortality in this report come from the official federal statistics on cancer, the U.S. Cancer Statistics (USCS) dataset (8). USCS includes cancer incidence data from CDC NPCR registries in 45 states and the District of Columbia (DC), NCI SEER program registries in 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah), and cancer mortality data from CDC NCHS NVSS.

Cancer incidence

Data on new cases of primary invasive gallbladder cancer (International Classification of Diseases for Oncology, Third Edition code C23.9; ref. 9) diagnosed during 1999 to 2011 were obtained from population-based cancer registries affiliated with the NPCR and SEER programs. In each state and DC, local and regional cancer data are reported to NPCR or SEER central cancer registries about all new diagnoses of cancer from patient records at such medical facilities as hospitals, physicians' offices, therapeutic radiation facilities, freestanding surgical centers, and

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pathology laboratories. The central cancer registries collate these data and use state vital records and the National Death Index to collect information about any cancer deaths that were not reported as cases. These data are submitted to CDC or NCI and combined into one dataset. Cancer registries demonstrated that cancer incidence was of high quality by meeting six USCS publication criteria (8).

Cancer mortality

Data on deaths occurring 1999–2011 from gallbladder cancer (International Classification of Diseases, 10th Revision code 23.0) were based on underlying cause of death in death certificates filed in the 50 states and DC and combined into one dataset by the NCHS NVSS (10).

Population estimates

Population denominators are race-specific, ethnicity-specific, and sex-specific county population estimates from the U.S. Census, modified by SEER and aggregated to the state and national level (11). Modifications incorporated bridged, single-race estimates that were derived from multiple-race categories in the Census (12) and accounted for known issues in certain counties, including adjustment for populations displaced in Louisiana, Alabama, Mississippi, and Texas in 2005 by hurricanes Katrina and Rita (11). The modified county-level population estimates, summed to the state and national levels, were used as denominators in rate calculations (11).

Statistical analysis

Five-year average annual rates for 2007 to 2011 per 100,000 population were age-adjusted (using 19 age groups) by the direct method to the 2000 U.S. standard population (13). Corresponding 95% confidence intervals (CI) were calculated as modified gamma intervals (14). Incidence rates for 2007 to 2011 were based on data from 50 cancer registries that met the USCS data-quality criteria for each year during 2007 to 2011, covering 99% of the U.S. population. Death rates for 2007 to 2011 were based on data from all states and DC. To determine differences between subgroups, rate ratios were calculated. The median age at diagnosis of cancer was calculated by race and ethnicity. State-specific age-adjusted gallbladder cancer incidence and death rates for 2007 to 2011 were mapped using quartiles as cutpoints.

Change in rates during 1999 to 2011 was calculated using joinpoint regression which involves fitting a series of joined straight lines on a logarithmic scale to the trends in the annual age-standardized rates (15); up to 2 joinpoints were allowed. The trend of the line segment was used to quantify the annual percent change (APC), and the t test was used to test whether the APC was statistically different from zero ($P < 0.05$). Rates were considered to increase or decrease if $P < 0.05$; otherwise, rates were considered stable. Trends in incidence rates during 1999–2011 were based on data from 41 cancer registries that met the USCS data-quality criteria for each year during 1999–2011, covering 89% of the U.S. population. Trends in death rates during 1999–2011 were based on data from all states and DC.

Gallbladder cancer incidence and death rates were analyzed by sex, racial and ethnic group, age group, U.S. Census region, U.S. state, county-level poverty, and percent of county population not born in the United States. Rates were calculated for each of five major racial/ethnic groups: non-Hispanic white, non-Hispanic black, non-Hispanic AI/AN, non-Hispanic Asian or Pacific Islander (API), and Hispanic. Information about race and Hispanic ethnicity was collected separately. An algorithm was applied to Hispanic ethnicity data to reduce misclassification of Hispanic persons as being of unknown ethnicity (16). To reduce misclassification of AI/AN race, first the Indian Health Service (IHS) patient registration database, which contains records of individuals who are members of federally recognized tribes, was linked to incidence data, and then rates for AI/AN were based on cases in counties covered by IHS Contract Health Service Delivery Area (CHSDA) because linkage studies have identified less misclassification of AI/AN race in CHSDA counties (17). Gallbladder cancer incidence and death rates among AI/AN were further analyzed by IHS region; because of small numbers of cases and deaths, annual rates were averaged over the 10-year period 1999–2011 (17). Information about CHSDA counties was not available for cases diagnosed in Kansas and Minnesota.

Gallbladder cancer incidence rates for 2007 to 2011 were analyzed by tumor characteristics, including stage, grade, and histology; these analyses excluded cases that were diagnosed only by death certificate or autopsy (2% of cases). Stage was classified using SEER Summary Stage 2000, which characterizes cancers as localized, regional, distant, or unknown stage; localized cancer is confined to the primary site, regional cancer has spread directly beyond the primary site (regional extension) or to regional lymph nodes, and distant cancer has spread to other organs (distant extension) or remote lymph nodes (18). Information about stage was not available for cases diagnosed in Minnesota.

Results

During 2007–2011, approximately 3,700 people were diagnosed with primary gallbladder cancer, and 2,000 people died from the disease each year in the United States (Table 1), for a rate of 1.13 cases and 0.62 deaths per 100,000 persons each year. Two thirds of gallbladder cancer cases and deaths occurred among women. AI/AN men and women experienced the highest gallbladder cancer incidence and death rates (3.15 cases and 1.56 deaths per 100,000), which were three times higher than among non-Hispanic white men and women, who experienced the lowest rates ($P < 0.05$). By county-level indicators, gallbladder cancer incidence and death rates were highest in counties where ≥13% households lived in poverty ($P < 0.05$) and in counties with ≥20% of residents who were born outside the United States ($P < 0.05$). Like many cancers, gallbladder cancer incidence and death rates increased with age and were highest in the oldest age group (9.85 cases and 6.74 deaths per 100,000); differences between men and women were highest in the youngest age group and attenuated with age. Median age at diagnosis of gallbladder cancer was older among non-Hispanic whites (median age at diagnosis = 73) than among other racial/ethnic groups (67–68; data not shown).

Gallbladder cancer incidence and death rates were higher in the Northeast and Midwest than in the South and West ($P < 0.05$; Table 1), although rates were also high in New Mexico (Fig. 1). By state, gallbladder cancer death rates ranged by 2-fold (from 0.37 to 0.82 deaths per 100,000) and incidence rates by more than 2-fold (from 0.71 to 1.87 cases per

Table 1. Number[a] and rate[b] of gallbladder cancer incident cases and deaths by demographic characteristics, United States, 2007–2011

	Incidence									Mortality								
	Overall			Males			Females			Overall			Males			Females		
	N	Rate	95% CI	N	Rate	95% CI	N	Rate	95% CI	N	Rate	95% CI	N	Rate	95% CI	N	Rate	95% CI
	3,669	1.13	(1.11–1.15)	1,151	0.82	(0.80–0.84)	2,519	1.38	(1.36–1.40)	2,028	0.62	(0.61–0.63)	655	0.47	(0.45–0.49)	1,372	0.74	(0.72–0.76)
Race/ethnicity[c]																		
Non-Hispanic white	2,442	0.95	(0.93–0.97)	781	0.70	(0.68–0.72)	1,661	1.15	(1.12–1.18)	1,410	0.54	(0.53–0.55)	456	0.41	(0.39–0.43)	954	0.64	(0.63–0.66)
Non-Hispanic black	500	1.65	(1.59–1.72)	160	1.37	(1.27–1.47)	340	1.88	(1.79–1.97)	263	0.88	(0.83–0.93)	86	0.75	(0.68–0.83)	177	0.98	(0.92–1.05)
Non-Hispanic AI/AN	32	3.15	(2.65–3.70)	11	2.51	(1.84–3.32)	20	3.61	(2.92–4.41)	16	1.56	(1.22–1.95)	4	0.93	(0.55–1.44)	12	2.03	(1.53–2.63)
Non-Hispanic API	161	1.33	(1.23–1.43)	56	1.09	(0.96–1.23)	105	1.52	(1.39–1.66)	90	0.76	(0.69–0.83)	38	0.74	(0.63–0.86)	52	0.77	(0.68–0.87)
Hispanic	511	2.06	(1.98–2.15)	134	1.28	(1.17–1.39)	378	2.70	(2.57–2.82)	241	1.01	(0.95–1.07)	70	0.70	(0.63–0.79)	172	1.25	(1.17–1.34)
Age, years																		
<45	99	0.06	(0.06–0.07)	30	0.04	(0.03–0.04)	69	0.08	(0.08–0.09)	33	0.02	(0.02–0.02)	10	0.01	(0.01–0.02)	23	0.03	(0.02–0.03)
45–54	318	0.71	(0.67–0.74)	99	0.45	(0.41–0.49)	219	0.96	(0.91–1.02)	141	0.31	(0.29–0.34)	43	0.19	(0.17–0.22)	97	0.42	(0.39–0.46)
55–64	708	2.00	(1.94–2.07)	225	1.32	(1.24–1.40)	484	2.64	(2.54–2.75)	361	1.01	(0.97–1.06)	128	0.74	(0.69–0.80)	234	1.26	(1.19–1.34)
65–74	982	4.76	(4.62–4.89)	337	3.53	(3.37–3.71)	645	5.81	(5.61–6.01)	535	2.58	(2.49–2.69)	186	1.95	(1.82–2.08)	350	3.13	(2.99–3.29)
75–84	1,036	7.90	(7.69–8.12)	332	6.11	(5.82–6.41)	703	9.19	(8.88–9.50)	596	4.51	(4.35–4.68)	198	3.61	(3.39–3.84)	398	5.15	(4.93–5.39)
≥85	526	9.85	(9.47–10.2)	128	7.44	(6.87–8.03)	398	11.00	(10.5–11.5)	362	6.74	(6.43–7.05)	91	5.24	(4.77–5.74)	271	7.45	(7.06–7.86)
Region																		
Northeast	849	1.33	(1.29–1.37)	265	0.99	(0.94–1.05)	584	1.60	(1.54–1.66)	452	0.71	(0.68–0.74)	146	0.55	(0.51–0.60)	306	0.82	(0.78–0.87)
Midwest	845	1.15	(1.11–1.18)	257	0.81	(0.77–0.86)	588	1.41	(1.36–1.47)	487	0.66	(0.63–0.69)	147	0.47	(0.44–0.51)	340	0.80	(0.77–0.84)
South	1,246	1.04	(1.01–1.06)	405	0.78	(0.75–0.81)	841	1.25	(1.21–1.29)	690	0.58	(0.56–0.60)	240	0.47	(0.44–0.50)	450	0.67	(0.64–0.70)
West	729	1.08	(1.05–1.12)	223	0.75	(0.71–0.80)	506	1.36	(1.31–1.42)	398	0.57	(0.54–0.60)	122	0.40	(0.37–0.43)	276	0.71	(0.67–0.75)
Percentage of families in county in poverty																		
<8%	1,023	1.10	(1.07–1.13)	317	0.79	(0.75–0.83)	705	1.34	(1.30–1.39)	588	0.60	(0.58–0.62)	179	0.42	(0.40–0.45)	409	0.73	(0.70–0.76)
8%–10.9%	851	1.02	(0.99–1.05)	275	0.76	(0.72–0.80)	576	1.24	(1.19–1.29)	482	0.55	(0.53–0.57)	160	0.42	(0.39–0.45)	321	0.65	(0.62–0.68)
11%–12.9%	690	1.15	(1.12–1.19)	223	0.86	(0.81–0.91)	467	1.39	(1.33–1.45)	404	0.66	(0.64–0.69)	136	0.52	(0.48–0.57)	268	0.77	(0.73–0.82)
≥13%	1,009	1.27	(1.23–1.30)	307	0.91	(0.86–0.96)	702	1.56	(1.50–1.61)	554	0.70	(0.67–0.72)	181	0.54	(0.51–0.58)	373	0.82	(0.78–0.86)
Percentage of county foreign born																		
<4.3%	892	1.02	(0.99–1.05)	285	0.74	(0.71–0.78)	607	1.24	(1.19–1.28)	524	0.57	(0.55–0.59)	168	0.43	(0.40–0.46)	355	0.69	(0.66–0.72)
4.3%–8.7%	878	1.09	(1.06–1.12)	288	0.83	(0.79–0.88)	590	1.30	(1.25–1.35)	497	0.60	(0.57–0.62)	161	0.46	(0.43–0.49)	336	0.70	(0.67–0.74)
8.8%–19.9%	807	1.08	(1.05–1.12)	255	0.80	(0.75–0.84)	552	1.32	(1.27–1.37)	450	0.59	(0.56–0.61)	149	0.45	(0.42–0.49)	301	0.69	(0.66–0.73)
≥20%	996	1.36	(1.32–1.40)	294	0.94	(0.89–0.99)	702	1.69	(1.64–1.75)	557	0.74	(0.71–0.77)	177	0.56	(0.52–0.59)	381	0.89	(0.85–0.93)

[a]Average annual number of cases or deaths. May not sum to total because of rounding.
[b]Per 100,000 persons, age-adjusted to the 2000 U.S. standard population.
[c]Incident case counts and rates are not presented for cases with unknown or other race. Rates for AI/AN are for AI/AN residing in CHSDA counties only.

100,000; Fig. 1). While high gallbladder cancer incidence rates were concentrated in the Northeast, high gallbladder cancer death rates were concentrated in the Midwest (Fig. 1). Among AI/AN men and women, gallbladder cancer incidence and death rates during 1999–2011 were highest in the Southwest IHS region, which includes New Mexico ($P < 0.05$), more than three times higher than in the Pacific Coast (Fig. 2).

About 11% of gallbladder cancers were diagnosed at an early stage, 43% after spread to regional organs or regional lymph nodes, and 42% after spread to distant organs or distant lymph nodes (Table 2). Fewer than 10% of gallbladder cancers were well-differentiated, 28% were moderately differentiated, 29% were poorly differentiated, and grade was unknown for about a third. Almost 90% of gallbladder cancers were adenocarcinomas, with most classified as adenocarcinoma NOS. By specific histologic type, 4% were typed as papillary adenocarcinomas, 3% as mucinous adenocarcinomas, 2% as signet ring cell carcinoma, and 2% as endocrine tumors.

During 1999–2011, incidence rates of gallbladder cancer decreased 0.5% per year from 1.52 to 1.38 cases per 100,000 among women but were stable among men (Table 3). Gallbladder cancer incidence rates decreased during 1999–2011 among Hispanic, API, and non-Hispanic white persons but increased 2.2% per year from 1.40 to 1.79 cases per 100,000 among black persons and did not change significantly among AI/AN persons (Table 3). By age, gallbladder cancer incidence rates increased 2.4% per year from 0.04 to 0.06 cases per

100,000 among those aged <45 years, were stable among those age 45 to 84 years, and decreased 0.9% per year from 11.74 to 9.93 cases per 100,000 among those aged ≥85 years (Table 3). By histology, rates increased 4.3% per year from 0.01 to 0.02 cases per 100,000 for endocrine tumors, decreased 4.0% per year from 0.05 to 0.03 cases per 100,000 for mucinous adenocarcinomas, and were stable for other histologic types (Fig. 3). Gallbladder cancer death rates decreased at the same rate (APC = −1.7) among men and women from 1999 to 2006, and then continued to decrease among women but remained level among men (Table 3). Gallbladder cancer death rates decreased 2.0% per year from 0.68 to 0.52 deaths per 100,000 during 1999–2011 among non-Hispanic white persons and 7.4% per year from 1.43 to 0.95 deaths per 100,000 during 1999–2004 then stabilizing among Hispanic persons (Table 3). Gallbladder cancer death rates increased 4.0% per year from 0.57 to 0.82 deaths per 100,000 among black men but were stable among black women (data not shown). By age, gallbladder cancer death rates were stable among those aged <65 years and decreased 1.0 to 1.8% per year among those aged ≥65 years (Table 3).

Discussion

Population-based data in this report show that gallbladder cancer incidence and death rates continue to decline among women but have leveled off among men overall and are increasing among black men. This report confirms that
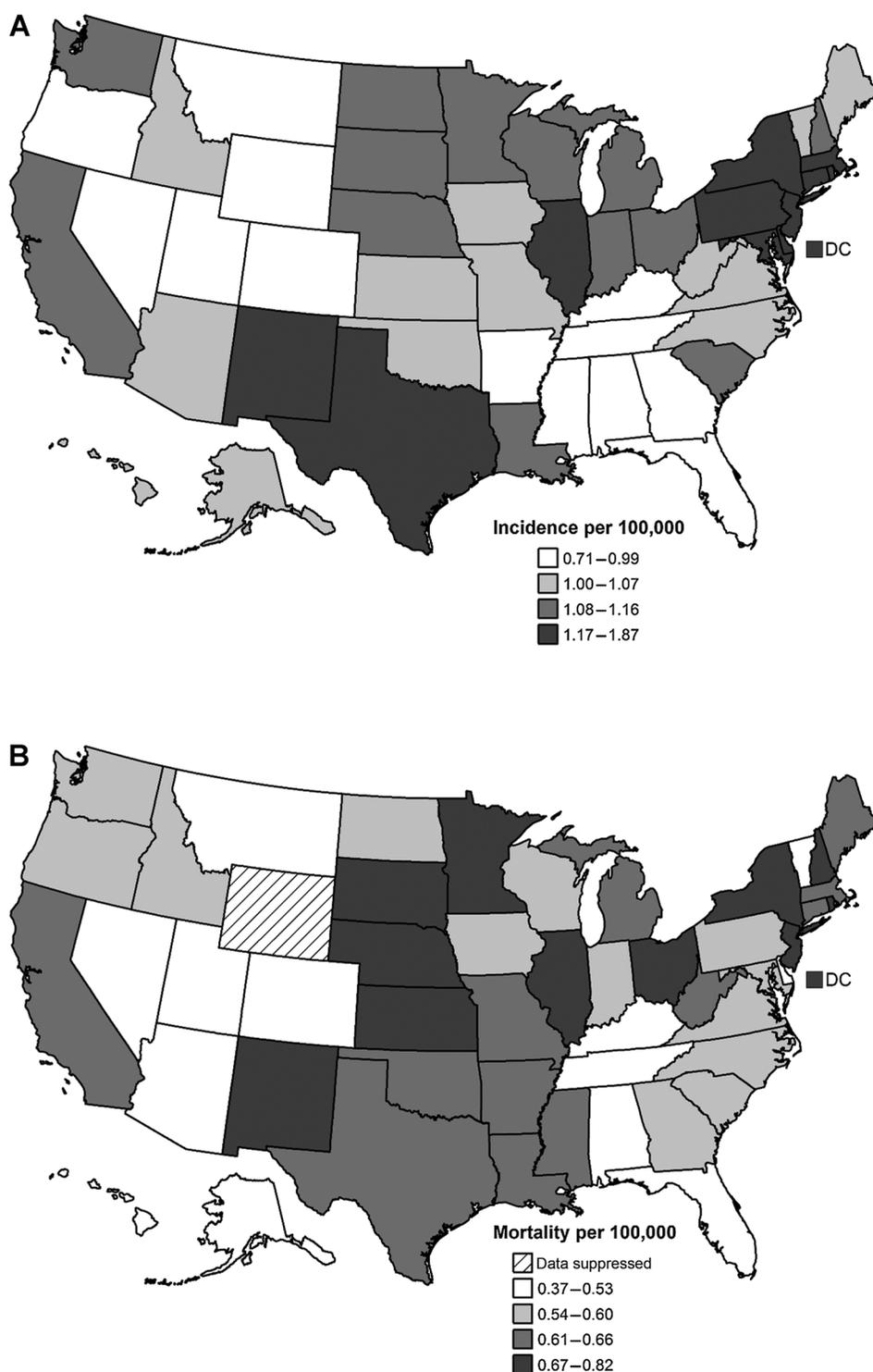
Figure 1.
Gallbladder cancer incidence rates (A) and death rates (B) for men and women combined, by state, 2007–2011. Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population.

women in the United States have higher incidence and death rates than men (19) but shows that because women experienced greater decreases in incidence and mortality during 1999–2011 than did men, the relative difference between men and women decreased slightly. The differences in trends among men and women point to the need to better under-

stand the causes of gallbladder cancer, which are not well known.

This report also confirms that gallbladder cancer incidence and death rates were highest among AI/AN men and women (5, 6). We found that gallbladder cancer incidence and death rates were highest among AI/AN men and women living in
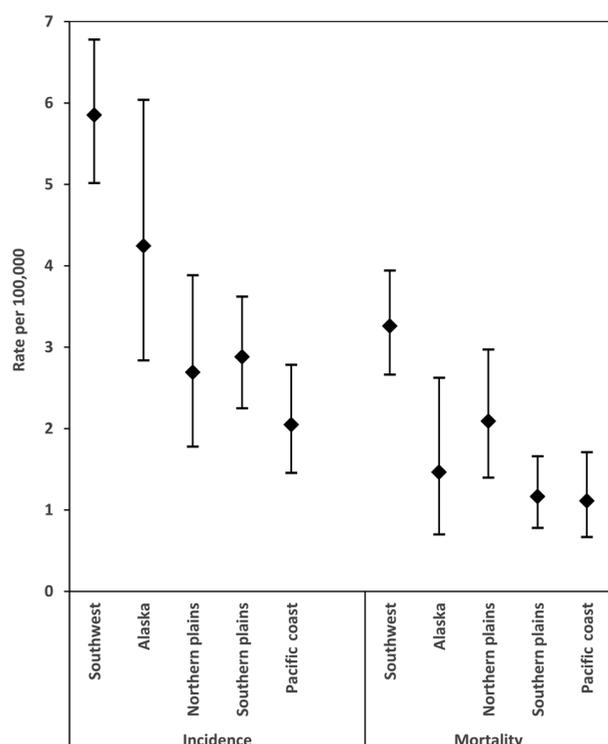
Figure 2.
Gallbladder cancer incidence and death rates among American Indians and Alaska Natives in counties covered by Contract Health Service Delivery Areas (CHSDA) by Indian Health Service Region, 1999–2011. Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population. Indian Health Service regions are defined as follows: Alaska (*AK*); Northern Plains (IL, *IN*, *IA*, *MI*, MN, *MT*, *NE*, ND, SD, *WI*, *WY*); Southern Plains (*OK*, KS, *TX*); Southwest (*AZ*, *CO*, NV, *NM*, *UT*); Pacific Coast (*CA*, *ID*, *OR*, *WA*, HI); and East (AL, AR, *CT*, DE, *FL*, GA, KY, *LA*, *ME*, MD, *MA*, MS, MO, NH, NJ, *NY*, *NC*, OH, *PA*, *RI*, *SC*, TN, VT, VA, WV, DC). States in italic have ≥1 county designated as CHSDA, and data from the cancer registry met USCS data quality criteria and had county-level information. Diamonds indicate rates, and vertical lines represent 95% CIs around the rates.

states in the Southwest IHS region (Arizona, Colorado, Nevada, New Mexico, and Utah). Studies show that countries or populations within countries that have high gallbladder cancer incidence also tend to have high prevalence of gallstones (cholelithiasis; refs. 1, 3). Evidence suggests that AI/AN men and women have higher rates of gallstones than do non-Hispanic white men and women (20). The presence of gallstones appears to increase the risk of developing gallbladder cancer, particularly for the AI/AN population compared with other racial and ethnic populations (21).

Cholelithiasis takes years to develop and generally precedes gallbladder cancer by about 20 years (3). Cholelithiasis, and its attendant chronic inflammation, is an important, but not sufficient, risk factor for gallbladder cancer. Although most (85%) people with gallbladder cancer have cholelithiasis, only a fraction (1%–3%) of people with cholelithiasis develop gallbladder cancer (3). While preventing cholelithiasis might prevent some cases of gallbladder cancer, some risk factors for cholelithiasis, such as older age, female sex, ethnic heritage, and family history, cannot be modified, and others such as obesity and poor diet may be difficult to

modify (2, 22). Further, we observed that gallbladder cancer incidence rates increased during 1999–2011 among people younger than 45 years; because cholelithiasis generally precedes gallbladder cancer by about 20 years, this increase could be due to other risk factors. Other risk factors for gallbladder cancer include obesity (particularly during adolescence), genetic factors, occupational exposures to carcinogens, and chronic infection (e.g., *Salmonella typhi*; refs. 2, 23). We observed that gallbladder cancer incidence and death rates were highest in counties with 20% or more of the population born outside the United States; this may be due to immigration from countries with environmental or genetic factors associated with higher rates of gallbladder cancer (1). As the evidence builds for what contributes to gallbladder cancer and as the proportion of persons who have these potential risk factors changes, it will be important to monitor

Table 2. Number[a] and rate[b] of gallbladder cancer incident cases[c] by tumor characteristics, United States, 2007–2011

	N (%)	Rate	95% CI
Summary stage			
Local	395 (11%)	0.12	(0.12–0.13)
Regional extension only	1,032 (30%)	0.33	(0.32–0.34)
Regional extension and/or regional lymph nodes involved	444 (13%)	0.14	(0.13–0.14)
Distant extension or distant lymph nodes involved	1,473 (42%)	0.46	(0.45–0.47)
Unknown	144 (4%)	0.05	(0.04–0.05)
Grade			
Well (I)	332 (9%)	0.10	(0.10–0.11)
Moderate (II)	1,007 (28%)	0.31	(0.3–0.32)
Poorly (III)	1,044 (29%)	0.32	(0.31–0.33)
Undifferentiated (IV)	69 (2%)	0.02	(0.02–0.02)
Unknown	1,099 (31%)	0.34	(0.33–0.35)
Histology			
Squamous cell carcinoma 8070–8078	48 (1%)	0.02	(0.01–0.02)
Adenocarcinoma 8140–8576	3,138 (88%)	0.97	(0.95–0.98)
Adenocarcinoma NOS 8140, 8141, 8143, 8147	2,412 (68%)	0.74	(0.73–0.76)
Adenocarcinoma intestinal type 8144	19 (1%)	0.01	(0.01–0.01)
Papillary adenocarcinoma 8260–8263	129 (4%)	0.04	(0.04–0.04)
Mucinous adenocarcinoma 8480–8481	109 (3%)	0.03	(0.03–0.04)
Signet ring cell carcinoma 8490	70 (2%)	0.02	(0.02–0.02)
Adenosquamous carcinoma 8560, 8562	83 (2%)	0.03	(0.02–0.03)
Endocrine tumors 8150–8157, 8240–8249, 8574	63 (2%)	0.02	(0.02–0.02)
Other adenocarcinoma	254 (7%)	0.08	(0.07–0.08)
All others	365 (10%)	0.11	(0.11–0.12)
Neoplasm unspecified 8000–8005	85 (2%)	0.03	(0.02–0.03)
Carcinoma NOS 8010–8015	196 (6%)	0.06	(0.06–0.06)
Carcinoma undifferentiated NOS 8020–8022	10 (0%)	0.00	(0–0)
Small cell 8041–8043	26 (1%)	0.01	(0.01–0.01)
Papillary carcinoma 8050–8052	<16 (0%)	0.00	(0–0)
Carcinosarcoma 8980–8982	<16 (0%)	0.00	(0–0)
Remaining values	30 (1%)	0.01	(0.01–0.01)

[a]Average annual number of cases.
[b]Per 100,000 persons, age-adjusted to the 2000 U.S. standard population.
[c]All analyses exclude cases identified only by death certificate or autopsy. Analysis by stage further excludes cases from Minnesota.

Table 3. APC[a] in gallbladder cancer incidence and death rates[b] by sex, racial and ethnic group, and age, United States, 1999–2011

	Incidence				Mortality			
	Joinpoint segments	Years in segment	APC	Rates at beginning and end of segment	Joinpoint segments	Years in segment	APC	Rates at beginning and end of segment
Overall	1	1999–2011	−0.4[c]	(1.23–1.14)	1	1999–2011	−1.4[c]	(0.75–0.61)
Sex								
Males	1	1999–2011	0.0	(0.86–0.84)	2	1999–2006	−1.7[c]	(0.52–0.45)
						2006–2011	1.0	(0.45–0.48)
Females	1	1999–2011	−0.5[c]	(1.52–1.38)	1	1999–2011	−1.7[c]	(0.93–0.72)
Race/ethnicity								
Non-Hispanic white	1	1999–2011	−0.9[c]	(1.10–0.95)	1	1999–2011	−2.0[c]	(0.68–0.52)
Non-Hispanic black	1	1999–2011	2.2[c]	(1.40–1.79)	1	1999–2011	0.8	(0.87–0.93)
Non-Hispanic AI/AN (CHSDA only)	1	1999–2011	−1.6	(4.17–2.67)	1	1999–2011	−3.0	(2.49–1.90)
Non-Hispanic API	1	1999–2011	−1.5[c]	(1.48–1.30)	1	1999–2011	−0.7	(0.90–0.76)
Hispanic	1	1999–2011	−1.8[c]	(2.54–1.95)	2	1999–2004	−7.4[c]	(1.43–0.95)
						2004–2011	0.9	(0.95–1.03)
Age, years								
<45	1	1999–2011	2.4[c]	(0.04–0.06)	1	1999–2011	−0.6	(0.02–0.02)
45–54	1	1999–2011	0.3	(0.67–0.70)	1	1999–2011	−1.6	(0.35–0.33)
55–64	1	1999–2011	−0.6	(2.25–2.02)	2	1999–2001	−8.7	(1.30–1.09)
						2001–2011	−0.7	(1.09–1.02)
65–74	2	1999–2001	−4.6	(5.31–4.81)	1	1999–2011	−1.0[c]	(3.00–2.54)
		2001–2011	0.0	(4.81–4.74)				
75–84	1	1999–2011	−0.6	(8.69–8.00)	1	1999–2011	−1.8[c]	(5.61–4.36)
≥85	1	1999–2011	−0.9[c]	(11.74–9.93)	1	1999–2011	−1.3[c]	(8.31–6.77)

[a]APC was calculated using joinpoint regression.
[b]Per 100,000 persons, age-adjusted to the 2000 U.S. standard population.
[c]APC was significantly different than 0 ($P < 0.05$).

rates of gallbladder cancer incidence and death rates to see if they also change.

We found that gallbladder cancer incidence rates decreased from 1999 to 2011 among non-Hispanic white, API, and Hispanic persons but increased among black persons, confirming findings from a report using SEER data (7). Reasons for this disparity are not yet known. Some studies suggest that the decline in gallbladder cancer incidence observed since the 1970s could be attributed to concomitant increases in cholecystectomies for early cholelithiasis (24, 25). In contrast, a study that found weak correlation between gallbladder cancer incidence and mortality rates with rates of inpatient laparoscopic cholecystectomy concluded that recent decreases in gallbladder cancer probably are due to factors other than cholecystectomy (26). Data from the Third National Health and Nutrition Examination Survey showed that non-Hispanic black persons had lower rates of cholelithiasis and cholecystectomy than did non-Hispanic white and Mexican American persons (27); this observation suggests that increases in gallbladder cancer incidence observed among black persons may be due to risk factors other than cholelithiasis.

The findings in this report are subject to several limitations. First, a considerable fraction (6%) of gallbladder cancer cases were assigned histology codes for cholangiocarcinoma, typically assigned to bile duct cancers. Because of potential misclassification, we did not include a category for cholangiocarcinoma in our main analysis but note that incidence rates increased 11% per year during 1999–2011 for the gallbladder cancer cases assigned with histology codes for cholangiocarcinoma. Data from SEER show that from 1975 to 1999, incidence of extrahepatic cholangiocarcinoma was stable, but incidence of intrahepatic cholangiocarcninoma increased 165% (28). However, an additional limitation is that analyses

of trends should be carefully interpreted; changes in incidence may result from changes in the prevalence of risk factors as well as from changes in the use of screening or diagnostic techniques.

A third limitation is that analyses based on race and ethnicity might be biased if race and ethnicity were misclassified. Particularly, rates may be underestimated for API, AI/AN, and Hispanics; however, efforts were made to ensure that this information was as accurate as possible. Analyses among AI/AN were restricted to those residing in CHSDA counties, which has been found to decrease misclassification of race and thus provide more accurate reflect rates (17). Fourth, analyses based on ethnicity are limited because grouping Hispanics as one ethnicity may mask important differences by country of origin (29). Fifth, county-level estimates were used for poverty and foreign-born, reflecting the area in which the individual cancer case resided, but not necessarily the status of that case.

This report provides data from U.S. population-based cancer registries that confirm that gallbladder cancer incidence and death rates are higher among women than men, highest among AI/AN men and women, and increase with age. We also found that gallbladder cancer incidence and death rates varied 2-fold by state and were higher in counties where 20% or more of the population was born outside the United States. Although overall gallbladder cancer incidence rates decreased during 1999–2011, incidence rates stabilized among men and increased among small subgroups, notably among black men and women, those aged <45 years and for cases with endocrine histology. Because effective strategies to prevent gallstones or gallbladder cancer have not yet been identified (2, 22), continued surveillance of gallbladder cancer incidence and mortality, particularly to monitor increases in subgroups, may provide clues to etiology and stimulate further research.
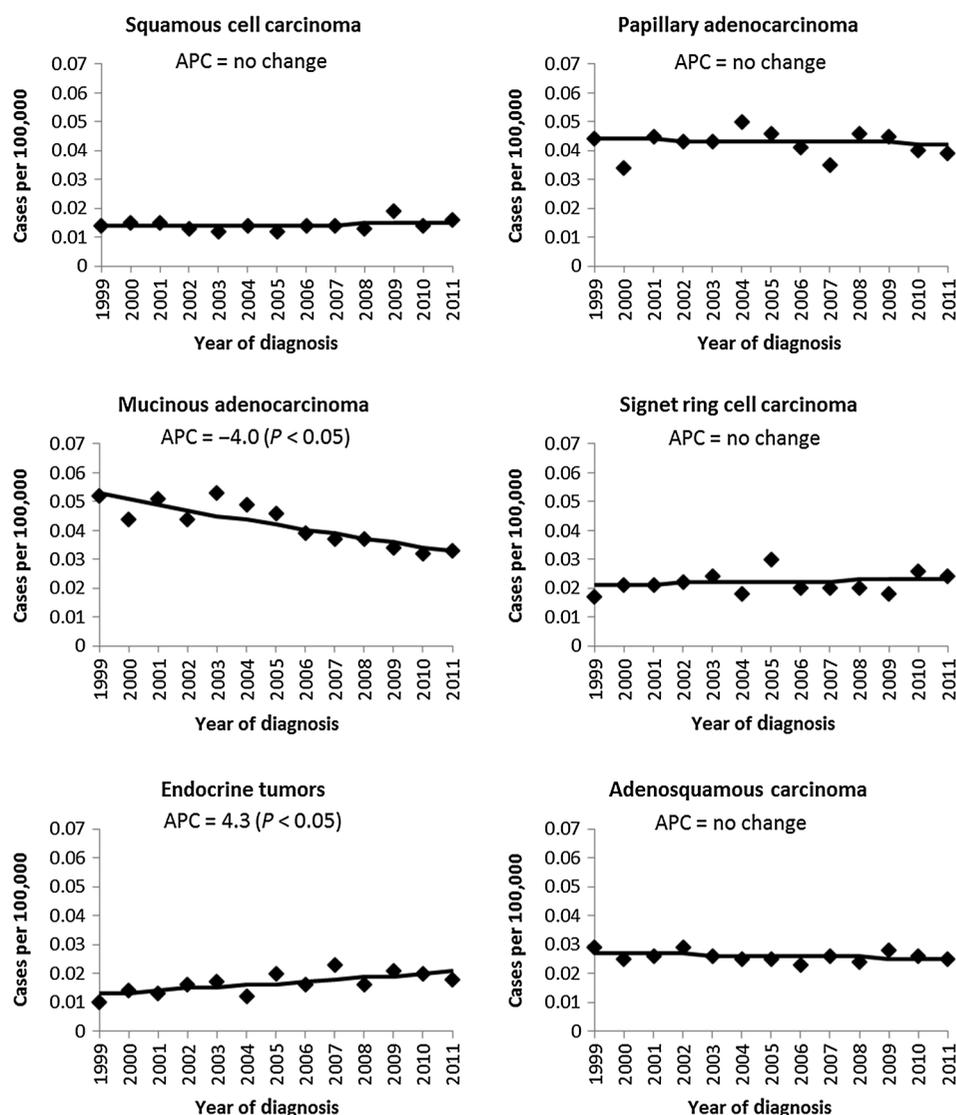
Figure 3.
Temporal trends in gallbladder cancer incidence rates by histology, US 1999–2011. Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population. APC was used to quantify the change in rates during 1999–2011 and was calculated using weighted least squares regression. Diamonds indicate rates, and lines represent trends.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' Contributions

Conception and design: S.J. Henley
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