2008

Gallbladder Cancer Incidence Among American Indians and Alaska Natives, US, 1999–2004

Shannon M. Lemrow
National Cancer Institute, lemrows@mail.nih.gov

David G. Perdue
University of Minnesota, perdu001@umn.edu

Sherri L. Stewart
Centers for Disease Control and Prevention, sstewart2@cdc.gov

Lisa C. Richardson
Centers for Disease Control and Prevention, LRichardson@cdc.gov

Melissa Jim
Centers for Disease Control and Prevention, melissa.jim@ihs.gov

See next page for additional authors

An Update on Cancer in American Indians and Alaska Natives, 1999–2004

Supplement to ***Cancer***

Gallbladder Cancer Incidence Among American Indians and Alaska Natives, US, 1999–2004

Shannon M. Lemrow, PhD[1]
David G. Perdue, MD, MSPH[2,3]
Sherri L. Stewart, PhD[4]
Lisa C. Richardson, MD, MPH[4]
Melissa A. Jim, MPH[4,5]
Helen T. French, BA[1]
Judith Swan, MHS[1]
Brenda K. Edwards, PhD[1]
Charles Wiggins, PhD, MPH[6]
Lois Dickie, CTR[1]
David K. Espey, MD[4,5]

[1] Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland.

[2] Division of Gastroenterology and Hepatology, Cancer Center, and Program in Health Disparities Research, University of Minnesota, Minneapolis, Minnesota.

[3] Minnesota Gasteroenterology, P.A., Minneapolis, Minnesota.

[4] Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

[5] Division of Epidemiology and Disease Prevention, Indian Health Service (IHS), Albuquerque, New Mexico.

[6] New Mexico Tumor Registry, University of New Mexico Cancer Center, Albuquerque, New Mexico.

This supplement was sponsored by Cooperative Agreement Number U50 DP424071-04 from the Centers for Disease Control and Prevention, Division of Cancer Prevention and Control.

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.

BACKGROUND. Gallbladder cancer (GBC) is rare; however, it disproportionately affects the American Indian and Alaska Natives (AI/AN) population. The purpose of the study was to characterize GBC among AI/AN in the US population.

METHODS. Cases of GBC diagnosed between 1999 and 2004 and collected by state-based cancer registries were included. Registry records were linked with Indian Health Service (IHS) administration records to decrease race misclassification of AI/AN. GBC rates and/or percent distributions for AI/AN and non-Hispanic whites (NHW) were calculated by sex, IHS region, age, and stage for all US counties and IHS Contract Health Service Delivery Area (CHSDA) counties, in which approximately 56% of US AI/AN individuals reside.

RESULTS. In CHSDA counties, the GBC incidence rate among AI/AN was 3.3 per 100,000, which was significantly higher than that among NHW ($P < .05$). Rates varied widely among IHS regions and ranged from 1.5 in the East to 5.5 in Alaska. Rates were higher among AI/AN females than males in all regions, except the Northern Plains. Higher percentages of GBC were diagnosed among AI/AN aged <65 years compared with NHW. GBC was most often diagnosed at the regional stage among AI/AN, whereas GBC was most often diagnosed at regional or distant stages among NHW.

CONCLUSIONS. To the authors' knowledge to date, this is the most comprehensive study of GBC incidence among AI/AN in the US. The accurate characterization of GBC in this population could help inform the development of interventions aimed at reducing morbidity and mortality from this disease. ***Cancer*** **2008;113(5 suppl):1266–73.** *Published 2008 by the American Cancer Society.**

KEYWORDS: American Indian/Alaska Native, surveillance, gallbladder cancer, regional stage, distant stage.

Gallbladder cancer (GBC) is an uncommon but highly fatal malignancy; a little over 3200 cases of GBC were diagnosed in the US in 2004.[1] Signs and symptoms of GBC, such as abdominal pain, are often vague. In many cases, GBC is found incidentally at the time of evaluation and surgical management for gallstones.[2] The lack of specific symptoms leads to frequent diagnosis at advanced stages of

Address for reprints: Sherri Stewart, PhD, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, 4770 Buford Highway, K-57, Atlanta, GA 30341; Fax: (770) 488-4335; E-mail: sstewart2@cdc.gov

Received May 5, 2008; accepted June 3, 2008.

Published 2008 by the American Cancer Society*
DOI 10.1002/cncr.23737
Published online 20 August 2008 in Wiley InterScience (www.interscience.wiley.com).

disease, when treatment options are limited. The overall median survival for advanced stage GBC is 2 months to 5 months.[3]

Because of the rarity of GBC, few studies have examined its burden in the US population. Recent studies using data from population-based cancer registries suggest that GBC incidence rates are relatively high among American Indian/Alaska Native (AI/AN) populations compared with other racial and ethnic populations,[4–6] with AI/AN individuals in New Mexico having the highest GBC incidence rates in the US.[6]

The AI/AN population in the US accounts for approximately 1% of the total population,[1] and cancer registries are known to under–report AI/AN race. A linkage study of registry data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program with the National Longitudinal Mortality Study (NLMS) data (a source of self-reported demographic data) concluded that AI/AN were considerably under–reported in SEER data by 66%, which was mainly because of SEER registries misclassifying AI/AN persons as white.[7]

The objective of the current study was to extend the work of previous studies that have reported a disproportionate burden of GBC in AI/AN populations by providing a more accurate description of GBC incidence among AI/AN. We describe GBC incidence for the US using the most geographically comprehensive population-based cancer registry data available, collected by the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the SEER program. NPCR and SEER registry data in this report are further enhanced through linkage with the Indian Health Service (IHS) patient registration database to reduce race misclassification of AI/AN. This study is part of a larger effort whose aim is to provide a more accurate description of cancer incidence among AI/AN.

MATERIALS AND METHODS

Detailed descriptions of the data sources and methods used for this analysis are found in another article in this supplement.[8]

Cases of GBC diagnosed between 1999 and 2004 were collected by cancer registries affiliated with the NPCR or SEER programs. GBC cases were defined according to the *International Classification of Diseases for Oncology*, third edition (C23.9)[9]; only invasive cases of GBC were included in analyses. Some histologies (lymphomas originating in the gallbladder, histologies involving hematopoietic diseases, mesotheliomas, and Kaposi sarcomas [M9050-9055, 9140, and 9590-9989]) were excluded.[9] Cases of GBC were included only from those states that met high–quality data criteria for publication.[1,8]

To reduce the misclassification of AI/AN race, all case records from each registry were linked with the IHS patient registration database to identify AI/AN cases misclassified as another race. The IHS provides medical services to AI/AN who are members of federally recognized tribes. Linkages were conducted using LinkPlus, a probabilistic linkage software program developed by the CDC that was applied to key patient identifiers.[10] Possible matches, requiring manual review, were examined independently by 2 reviewers, and when necessary, adjudicated by a third reviewer. Information obtained from the linkage was combined with the multiple race fields coded in cancer registry records. If a registry record was coded white or unknown and was identified as a positive IHS match, the case was reclassified as AI/AN for this analysis.[8]

GBC counts, incidence rates, 95% confidence intervals, and rate ratios were calculated using SEER*Stat Software (version 6.3.6).[11] Analyses were performed for all US counties combined meeting quality criteria and for Contract Health Service Delivery Area (CHSDA) counties that, in general, contain federally recognized tribal lands or are adjacent to tribal lands.[8] Analyses restricted to CHSDA counties are presented for the purpose of offering improved accuracy in interpreting cancer statistics for AI/AN.[8] For this report, registries in 46 states and the District of Columbia contributed data to the "All counties" analysis, and 33 registries contributed data to the CHSDA county analyses.[8] Approximately 56% of the US AI/AN population reside in CHSDA counties. This proportion varies by IHS region: Alaska: 100%; East: 15.4%; Northern Plains: 51.5%; Southern Plains: 69.0%; Pacific Coast: 45.0%; and Southwest: 88.1% (in each region the proportion of AI/AN in CHSDA counties to AI/AN in all counties.) Figure 1 illustrates the states included in this analysis by CHSDA county.

Denominators for rate calculations are from the US Census Bureau and are slightly modified by SEER to produce potentially more accurate rates.[1] All rates are expressed per 100,000 persons, and are age-adjusted to the 2000 US standard population by 19 age groups (<1, 1-4, 5-9 years, etc) by the direct method.[1] Rates are stratified by race (AI/AN and non-Hispanic white [NHW]), sex, IHS region (Northern Plains, Alaska, Southern Plains, Pacific Coast, East, and Southwest [Fig. 1]), and SEER Summary Stage. SEER Summary Stage is a staging system routinely used by cancer registries; in SEER Summary Stage, a localized stage refers to cancer that is con-

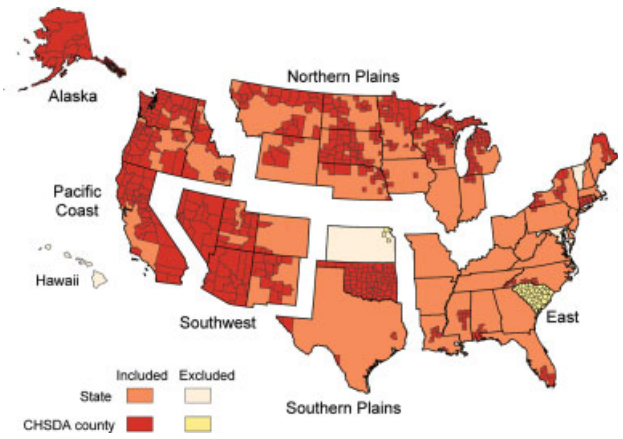

FIGURE 1. States and Contract Health Service Delivery Areas (CHSDA) counties by Indian Health Service region.

fined to the gallbladder, regional stage refers to cancer that has spread directly beyond the gallbladder or to regional lymph nodes, and distant stage refers to cancer that has spread to other organs.[12] The stage presentation is restricted to cases from 2001 to 2003 because of major differences in SEER Summary Stage coding for cases diagnosed before 2001 and after 2003.[12] Frequency calculations and rates are shown for age analyses (<50, 50-64, and 65 + years) and are stratified by race and sex. Age groups were selected with consideration of age-related influences, such as Medicare benefits.

RESULTS

Overall, from 1999 through 2004 the GBC rate among AI/AN in all counties of the US was 2.1 per 100,000 (Table 1). Rates varied considerably among IHS regions. They were lowest in the East (0.5) and highest in Alaska (5.5). In most IHS regions, GBC rates were higher among AI/AN females than among AI/AN males, with the exception of the East region, in which the GBC incidence rate was the same among AI/AN males and females (0.5). The highest regional rates among AI/AN males and females individually were found in Alaska (4.6 for males and 6.9 for females). Overall, the GBC incidence rate was significantly higher among AI/AN (2.1) than for NHW (1.0) ($P < .05$). Significantly higher rates among AI/AN compared with NHW were also observed in all IHS regions, with the exception of the Pacific Coast region, where the difference was not statistically significant. For the CHSDA county analysis, the overall GBC incidence rate was higher, as expected, at 3.3 per 100,000. Incidence patterns similar to those in the all-counties analysis were present in the CHSDA county analysis. Incidence rates varied widely by region (range, 1.5-5.5), and they were higher among AI/AN females than among AI/AN males (with the exception of the Northern Plains region). Finally, the overall (3.3 for AI/AN, 0.9 for NHW; $P < .05$) and regional AI/AN rates were significantly higher than NHW rates for all IHS regions except the East region.

In CHSDA counties, the majority of AI/AN (65.3%) and NHW (77.0%) were diagnosed at age ≥65 years (Table 2). For those aged ≥65 years, the AI/AN incidence rate was significantly higher than that for NHW (20.0 compared with 5.5; $P < .05$). Approximately one-quarter (25.9%) of the diagnoses occurred among AI/AN ages 50 years to 64 years, and nearly one-tenth (8.8%) occurred among AI/AN aged <50 years. These percentages were higher than those found among NHW for the same age groups (19.2% for ages 50 years-64 years, and 3.7% for ages <50 years). The incidence rate for AI/AN aged 50 years to 64 years was significantly higher than that for NHW (3.9 vs 1.2; $P < .05$). As with the regional analyses, AI/AN and NHW females had higher incidence rates than AI/AN and NHW males for every age category.

GBC was diagnosed most often at regional stages among AI/AN (36.4%) in CHSDA counties (Table 3). Among NHW, GBC diagnoses were more often of regional (33.3%) or distant (33.3%) stage. Slightly higher percentages of GBC were diagnosed at a localized stage compared with NHW (27.3% vs 22.2%). Incidence rates were higher among AI/AN than for NHW for localized, regional, and distant stage disease.

DISCUSSION

This study yielded several important and novel findings. Consistent with other studies, significantly higher incidence rates of GBC were found among AI/AN than among NHW, AI/AN GBC rates were almost always higher among AI/AN females than for AI/AN males, and AI/AN were more often diagnosed at younger ages than were NHW. Novel findings of this study include the observation of considerable regional variation of GBC incidence rates by IHS region, and greater percentages of localized disease diagnoses among AI/AN than for NHW.

The higher GBC rates noted among AI/AN in this study and others may be explained in part by the relation between GBC and gallstone formation. Gallstones contribute to the development of GBC by causing chronic inflammation that rarely leads to malignant transformation.[2,13] It has also been sug-

TABLE 1
Gallbladder Cancer Incidence by Sex and Indian Health Service Region for American Indians/Alaska Natives[a] and Non-Hispanic Whites, US, 1999-2004

		CHSDA Counties						All Counties					
IHS Region	Sex	AI/AN Count	AI/AN Rate[b]	95% CI for AI/AN Rate	NHW Rate[b]	Rate Ratio[c] (AI/AN:NHW)	95% CI for Rate Ratio	AI/AN Count	AI/AN Rate[b]	95% CI for AI/AN Rate	NHW Rate[b]	Rate Ratio[c] (AI/AN:NHW)	95% CI for Rate Ratio
Northern Plains	Both sexes	21	2.6	1.6-4.0	1.0	2.48[c]	1.49-3.86	25	2.0	1.3-3.0	1.1	1.77‡	1.11-2.67
	Male	10	2.7	1.3-5.2	0.7	3.97[c]	1.79-7.67	11	1.8	0.9-3.3	0.8	2.36‡	1.12-4.35
	Female	11	2.5	1.2-4.5	1.3	1.89	0.91-3.44	14	2.1	1.1-3.5	1.4	1.47	0.77-2.49
Alaska[d]	Both sexes	17	5.5	3.1-8.9	0.8	6.65[c]	2.94-15.85	17	5.5	3.1-8.9	0.8	6.65[c]	2.94-15.85
	Male	~	4.6	1.2-10.8	0.6	7.38[c]	1.48-30.52	~	4.6	1.2-10.8	0.6	7.38[c]	1.48-30.52
	Female	12	6.9	3.5-12.0	0.9	7.91[c]	2.81-25.97	12	6.9	3.5-12.0	0.9	7.91[c]	2.81-25.97
Southern Plains	Both sexes	25	2.1	1.3-3.1	0.8	2.48[c]	1.54-3.78	30	1.8	1.2-2.6	0.8	2.16[c]	1.42-3.12
	Male	6	1.5	0.5-3.2	0.6	2.29	0.72-5.26	8	1.4	0.5-2.8	0.6	2.15	0.83-4.32
	Female	19	2.6	1.6-4.1	1.0	2.65[c]	1.53-4.31	22	2.3	1.4-3.4	1.0	2.26[c]	1.40-3.45
Pacific Coast	Both sexes	17	1.5	0.8-2.4	0.9	1.72	0.95-2.79	20	1.0	0.6-1.5	0.8	1.17	0.69-1.83
	Male	~	0.8	0.2-2.1	0.6	1.43	0.35-3.65	~	0.6	0.2-1.3	0.5	1.10	0.33-2.54
	Female	13	2.0	1.0-3.5	1.1	1.80	0.92-3.11	15	1.3	0.7-2.1	1.1	1.19	0.65-1.98
East	Both sexes	~	1.6	0.4-3.9	1.0	1.65	0.42-4.06	9	0.5	0.2-0.9	1.1	0.43[c]	0.19-0.82
	Male	~	1.3	0.0-5.5	0.8	1.64	0.04-7.18	~	0.5	0.1-1.2	0.8	0.56	0.11-1.53
	Female	~	1.8	0.4-5.2	1.1	1.61	0.31-4.55	6	0.5	0.2-1.0	1.3	0.38[c]	0.14-0.83
Southwest	Both sexes	86	5.5	4.4-6.9	0.8	6.98[c]	5.40-8.89	88	5.1	4.0-6.3	0.8	6.16[c]	4.82-7.74
	Male	29	4.1	2.7-5.9	0.7	6.21[c]	3.91-9.39	29	3.7	2.4-5.3	0.7	5.49[c]	3.50-8.18
	Female	57	6.6	4.9-8.5	0.9	7.20[c]	5.24-9.68	59	6.1	4.6-7.9	1.0	6.36[c]	4.71-8.40
Total	Both sexes	170	3.3	2.8-3.8	0.9	3.59[c]	3.04-4.22	189	2.1	1.8-2.5	1.0	2.11[c]	1.80-2.44
	Male	55	2.5	1.8-3.3	0.7	3.69[c]	2.69-4.92	61	1.6	1.2-2.1	0.7	2.18[c]	1.62-2.85
	Female	115	3.9	3.2-4.7	1.1	3.50[c]	2.85-4.23	128	2.5	2.1-3.0	1.2	2.06[c]	1.71-2.46

Source: Cancer registries in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

CHSDA indicates Contract Health Service Delivery Areas; HIS, Indian Health Service; AI/AN, American Indians/Alaska Natives; 95% CI, 95% confidence interval; NHW, non-Hispanic whites.

[a] AI/AN race is reported by NPCR and SEER registries or through linkage with the IHS patient registration database. Hispanic origin is not mutually exclusive from the race categories (white, black, Asian/Pacific Islander).

[b] Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population (19 age groups-Census P25-1130).

[c] The rate ratio is statistically significant ($P < .05$).

[d] Rates and rate ratios for Alaska in the CHSDA counties section are the same as those in the "All Counties" section because all counties in Alaska are CHSDA counties.

~ Counts <6 are suppressed.

Years of data and registries used: 1999-2004 (41 states and the District of Columbia): Alabama,* Alaska,* Arkansas, Arizona,* California,* Colorado,* Connecticut,* Delaware, District of Columbia, Florida,* Georgia, Hawaii, Idaho,* Illinois, Indiana,* Iowa,* Kentucky,* Louisiana,* Maine,* Massachusetts,* Michigan,* Minnesota,* Missouri, Montana,* North Carolina,* Nebraska,* Nevada,* New Hampshire, New Jersey, New Mexico,* New York,* Ohio, Oklahoma,* Oregon,* Pennsylvania,* Rhode Island,* Texas,* Utah,* Washington,* West Virginia, Wisconsin,* and Wyoming*; 1999 and 2002-2004: North Dakota*; 2001-2004: South Dakota*; 2003-2004: Mississippi* and Virginia; 2004: Tennessee. *States with at least 1 county designated as CHSDA.Percent regional coverage of AI/AN in CHSDA counties to AI/AN in all counties: Alaska: 100%; East: 15.4%; Northern Plains: 51.5%; Southern Plains: 69.0%; Pacific Coast: 45.0%; Southwest: 88.1%.

TABLE 2
Gallbladder Cancer Incidence Rates[a] and Percent Distribution by Age and Sex for American Indians/Alaska Natives and Non-Hispanic Whites, CHSDA Counties, US, 1999-2004

	<50 Years				50-64 Years				65+ Years			
Gender	Count	Row[b]	Rate[a]	95% CI	Count	Row[b]	Rate[a]	95% CI	Count	Row[b]	Rate[a]	95% CI
American Indian/Alaska Native												
Both sexes	15	8.8%	0.2	0.1-0.4	44	25.9%	3.9[c]	2.9-5.3	111	65.3%	20.0[c]	16.4-24.2
Male	6	10.9%	0.2	0.1-0.4	12	21.8%	2.3[c]	1.2-4.0	37	67.3%	15.6[c]	10.8-21.9
Female	9	7.8%	0.3	0.1-0.5	32	27.8%	5.4[c]	3.7-7.7	74	64.3%	22.9[c]	17.9-28.8
Non-Hispanic White												
Both sexes	98	3.7%	0.1	0.0-0.1	503	19.2%	1.2	1.1-1.3	2017	77.0%	5.5	5.3-5.8
Male	28	3.5%	0.0	0.0-0.0	169	20.9%	0.8	0.7-1.0	610	75.6%	4.1	3.8-4.5
Female	70	3.9%	0.1	0.1-0.1	334	18.4%	1.6	1.4-1.7	1407	77.7%	6.5	6.2-6.9

Source: Cancer registries in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

CHSDA indicates Contract Health Service Delivery Areas; 95% CI, 95% confidence interval.

[a] Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population (19 age groups-Census P25-1130).

[b] Percents may not add to 100.0% due to rounding

[c] Indicates AI/AN rate is statistically significantly higher than the non-Hispanic white (NHW) rate.

Years of data and registries used: 1999-2004 (41 states and the District of Columbia): Alabama,* Alaska,* Arkansas, Arizona,* California,* Colorado,* Connecticut,* Delaware, District of Columbia, Florida,* Georgia, Hawaii, Idaho,* Illinois, Indiana,* Iowa,* Kentucky,* Louisiana,* Maine,* Massachusetts,* Michigan,* Minnesota,* Missouri, Montana,* North Carolina,* Nebraska,* Nevada,* New Hampshire, New Jersey, New Mexico,* New York,* Ohio, Oklahoma,* Oregon,* Pennsylvania,* Rhode Island,* Texas,* Utah,* Washington,* West Virginia, Wisconsin,* and Wyoming*; 1999 and 2002-2004: North Dakota*; 2001-2004: South Dakota*; 2003-2004: Mississippi* and Virginia; 2004: Tennessee. *States with at least 1 county designated as CHSDA.

TABLE 3
Gallbladder Cancer Incidence and Age-adjusted Percent Distributions by Summary Stage[a] and Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites, CHSDA Counties, US, 2001-2003

	Localized				Regional				Distant				Unstaged				All			
Race	Count	Rate[b]	95% CI	%[c]	Count	Rate[b]	95% CI	%[c]	Count	Rate[b]	95% CI	%[c]	Count	Rate[b]	95% CI	%[c]	Count	Rate[b]	95% CI	%[c]
AI/AN	24	0.9	0.6-1.3	27.3%	34	1.2	0.8-1.7	36.4%	27	0.9	0.6-1.3	27.3%	8	0.3	0.1-0.6	9.1%	93	3.3	2.7-4.1	100%
NHW	228	0.2	0.1-0.2	22.2%	487	0.3	0.3-0.4	33.3%	463	0.3	0.3-0.4	33.3%	130	0.1	0.1-0.1	11.1%	1308	0.9	0.9-1.0	100%

Source: Cancer registries in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

CHSDA indicates Contract Health Service Delivery Areas; 95% CI, 95% confidence interval; AI/AN, American Indian/Alaska Native; NHW, non-Hispanic white.

[a] SEER Summary Stage 2000 was used.

[b] Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population (19 age groups-Census P25-1130).

[c] Percent distribution is age-adjusted to the 2000 US standard population. Some age groups may have been combined to manage small cell counts.

Years of data and registries used: 1999-2004 (41 states and the District of Columbia): Alabama,* Alaska,* Arkansas, Arizona,* California,* Colorado,* Connecticut,* Delaware, District of Columbia, Florida,* Georgia, Hawaii, Idaho,* Illinois, Indiana,* Iowa,* Kentucky,* Louisiana,* Maine,* Massachusetts,* Michigan,* Minnesota,* Missouri, Montana,* North Carolina,* Nebraska,* Nevada,* New Hampshire, New Jersey, New Mexico,* New York,* Ohio, Oklahoma,* Oregon,* Pennsylvania,* Rhode Island,* Texas,* Utah,* Washington,* West Virginia, Wisconsin,* and Wyoming*; 1999 and 2002-2004: North Dakota*; 2001-2004: South Dakota*; 2003-2004: Mississippi* and Virginia; 2004: Tennessee. *States with at least 1 county designated as CHSDA.

gested that the chronic inflammation caused by gallstones may act as a promoter for some other carcinogenic exposure in GBC.[2] In AI/AN, the presence of gallstones appears to increase the risk of developing GBC in particular for this population compared with other racial and ethnic populations.[14] In addition, evidence suggests that AI/AN have higher rates of gallstones than do NHW. The Strong Heart Study, which examined gallbladder disease (defined as ultrasound evidence of gallstones or cholecystectomy) among > 3000 members of multiple AI tribes, reported prevalence rates of 64.1% among females and 29.5% for males.[15] Similar studies have found gallbladder disease prevalence rates to be much lower in NHW populations (16.6% and 8.6%, respectively, among females and males).[16]

Our findings confirm those from previous studies that have found higher rates of GBC among females than among males.[4,5,17] Female sex and parity are known risk factors for gallbladder disease and GBC.[18] Higher rates of gallstone formation among females may be related to the hormonal environment. Females have a higher prevalence of gallstones and are prone to develop biliary sludge and/or gallstones during pregnancy.[19] Compelling evidence of the association of parity with GBC was reported in the SEARCH study, which concluded that females with >3 pregnancies had more than twice the risk of developing gallstones than did females with only 1 pregnancy.[18] Although oral contraceptives have been implicated in the carcinogenesis of GBC, a conclusive association has not been proven.[2,20] There is also insufficient evidence for a conclusive association with hormone replacement therapy.[18,20]

The variation in GBC incidence by IHS region reported herein may be related to lifestyle and behavioral factors, such as obesity and tobacco use. Recent reviews have reported an association between obesity and GBC,[13,18,21] and multiple studies have reported higher obesity rates among AI/AN than for other racial and ethnic populations.[22–25] Current estimates using the CDC's Behavioral Risk Factor Surveillance System (BRFSS) data show that AI/AN have a higher prevalence of obesity (body mass index >30 kg/m^2) than do NHW in all IHS regions, although there was no discernable pattern by IHS region.[22]

Tobacco use has also been associated with GBC.[26,27] Chow et al[26] reported a 50% excess risk of biliary tract cancer, including GBC, among tobacco users. BRFSS data demonstrate that current smoking rates vary widely by IHS region, being highest in the Northern Plains (40.1%) and Alaska (39.4%) and lowest in the Southwest (21.0%).[22] According to the 2004 Report of the Surgeon General on health consequences of smoking, there is insufficient evidence to allow an inference of a direct causal relation between smoking and GBC[28]; therefore, tobacco may act synergistically with other risk factors such as obesity to increase the risk of developing GBC. Other health behaviors that increase the risk of developing cancer, such as low levels of physical activity, are also found more often among AI/AN.[22]

AI/AN were more often diagnosed with regional stage GBC than were NHW. As is the case with most cancers, early diagnosis is a key factor in survival from GBC. Treatment with surgery becomes more difficult with regional GBC, and GBC does not respond well to currently available systemic chemotherapy.[2] Patients with advanced disease have a 1-year survival rate of <5%,[29] and such patients are generally treated with palliation for relief of pain, jaundice, and bowel obstruction.[2] It is unlikely that the increased rates of cholecystectomy explain the increased incidence of localized GBC in AI/AN. A study examining this correlation in a Scottish population found that incidence of GBC was not increased with increased cholecystectomy, nor was survival improved, suggesting that incidental discovery of early–stage cancer during cholescystectomy is unlikely.[30]

Similar to 1 other report,[6] this study found that GBC was diagnosed in higher percentages in younger age groups of AI/AN compared with NHW. Earlier age of onset for GBC has also been reported in India,[31] and GBC was found to be correlated with gallstone formation in this population. Persons with gallstones were found to present with GBC at an age that was 5.6 years younger than those with no gallstones. The authors also concluded that GBC was associated with lower socioeconomic status independent of gallstones. A similar association between GBC incidence and socioeconomic status was found in a Scottish population[30]; males and females living in the most economically deprived areas of Scotland were found to have a higher incidence of GBC. AI/AN in the US tend to have lower socioeconomic status than do NHW.[32] Similar to smoking, lower socioeconomic status may act with other risk factors to increase the risk of developing GBC among AI/AN populations.

GBC is an aggressive disease that carries a poor prognosis, and significant improvements in survival are unlikely to be noted with currently available chemotherapeutic agents.[2] Several tumor suppressor and oncogenes, such as p53 and K-*ras*, have been shown to be mutated or overexpressed in GBC.[33,34] To our knowledge, the contribution of these genetic risk factors is currently unknown in AI/AN popula-

tions. Future molecular biologic studies may lead to the identification of targeted therapies for GBC. At this time, careful preoperative imaging for all patients undergoing gallbladder removal and appropriate workup for all suspicious lesions, especially for populations at greater risk such as AI/AN, may offer the best options for improved survival.[2]

Several limitations need to be considered when interpreting the results of the current study. Although data linkages between central cancer registry data and IHS enrollment data reduced racial misclassification for AI/AN living in CHSDA counties, our algorithm does not correct for misclassification of those individuals who are not members of federally recognized tribes who are not in the IHS database. Many AI/AN who live primarily in urban non-CHSDA areas are underrepresented, and thus the findings are not generalizable to all AI/AN in the US or in individual IHS regions, especially those, such as the East region, with a small overall proportion living in CHSDA counties.

In summary, to our knowledge this is the most comprehensive analysis of GBC incidence among AI/AN in the US population. These findings provide a basis for healthcare providers, cancer control planners, and community outreach professionals to begin to address the needs of the AI/AN population regarding this disease. Future efforts that ensure high-quality data availability from all population-based cancer registries in the US, and the further development and evaluation of methodologies to reduce AI/AN misclassification in cancer registries, would greatly benefit the description of GBC, as well as other cancers, among all AI/AN.

REFERENCES

1. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 2004 Incidence. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2007.
2. Bartlett D, Ramanathan R, Deutsch M. Cancer of the biliary tree. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology. 7th ed. Philadelphia: Lippincott, Williams, and Wilkins, 2005:1009-1035.
3. Kiran RP, Pokala N, Dudrick SJ. Incidence pattern and survival for gallbladder cancer over 3 decades—an analysis of 10301 patients. *Ann Surg Oncol*. 2007;14:827-832.
4. Goodman MT, Yamamoto J. Descriptive study of gallbladder, extrahepatic bile duct, and ampullary cancers in the United States, 1997-2002. *Cancer Causes Control*. 2007;18: 415-422.
5. Paltoo DN, Chu KC. Patterns in cancer incidence among American Indians/Alaska Natives, United States, 1992-1999. *Public Health Rep*. 2004;119:443-451.
6. Barakat J, Dunkelberg JC, Ma TY. Changing patterns of gallbladder carcinoma in New Mexico. *Cancer*. 2006;106: 434-440.
7. Clegg LX, Reichman ME, Hankey BF, et al. Quality of race, Hispanic ethnicity, and immigrant status in population-based cancer registry data: implications for health disparity studies. *Cancer Causes Control*. 2007;18:177-187.
8. Espey DK, Wiggins C, Jim M, Miller B, Johnson C, Becker TM. Methods for improving cancer surveillance data in American Indian and Alaska Native populations. *Cancer*. 2008;113(5 suppl):1120-1130.
9. Fritz A, Percy C, Jack A. International Classification of Diseases of Oncology. Geneva: World Health Organization, 2000.
10. Centers for Disease Control and Prevention. LinkPlus: A suite of publicly available software programs for collecting and processing cancer registry data. Atlanta: Centers for Disease Control and Prevention; 2005. Available at: http://www.cdc.gov/cancer/npcr/tools/registryplus/lp.htm. Accessed on July 1, 2008.
11. Surveillance Research Program. SEER*Stat software. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch; 2007. Available at: http://www.seer.cancer.gov/seerstat. Accessed on July 1, 2008.
12. Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA. SEER Summary Staging Manual-2000: Codes and Coding Instructions. NIH Pub. No. 01–4969. Bethesda, MD: National Cancer Institute; 2001.
13. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer*. 2006;118:1591-1602.
14. Lowenfels AB, Lindstrom CG, Conway MJ, Hastings PR. Gallstones and risk of gallbladder cancer. *J Natl Cancer Inst*. 1985;75:77-80.
15. Everhart JE, Yeh F, Lee ET, et al. Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. *Hepatology*. 2002;35:1507-1512.
16. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology*. 1999;117:632-639.
17. Pandey M, Sharma LB, Singh S, Shukla VK. Erythrocyte membrane fatty acid profile and saturation index in gallbladder carcinogenesis: a case-control study. *World J Surg Oncol*. 2003;1:5.
18. Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst*. 1997;89:1132-1138.
19. Attili AF, Capocaccia R, Carulli N, et al. Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. *Hepatology*. 1997;26:809-818.
20. [No authors listed.] Combined oral contraceptives and gallbladder cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Epidemiol*. 1989;18:309-314.
21. Moerman CJ, Bueno-de-Mesquita HB. The epidemiology of gallbladder cancer: lifestyle related risk factors and limited surgical possibilities for prevention. *Hepatogastroenterology*. 1999;46:1533-1539.
22. Steele C, Cardinez C, Richardson L, Tom-Orme L, Shaw K. Surveillance for health behaviors of American Indians and Alaska Natives—findings from the Behavioral Risk Factor Surveillance System, 2000–2006. *Cancer*. 2008; 113(5 suppl):1131-1141.

23. Denny CH, Taylor TL. American Indian and Alaska Native health behavior: findings from the behavioral risk factor surveillance system, 1992-1995. *Ethn Dis*. 1999;9:403-409.
24. Denny CH, Holtzman D, Goins RT, Croft JB. Disparities in chronic disease risk factors and health status between American Indian/Alaska Native and White elders: findings from a telephone survey, 2001 and 2002. *Am J Public Health*. 2005;95:825-827.
25. Doshi SR, Jiles R. Health behaviors among American Indian/Alaska Native women, 1998-2000 BRFSS. *J Womens Health (Larchmt)*. 2006;15:919-927.
26. Chow WH, McLaughlin JK, Hrubec Z, Fraumeni JF Jr. Smoking and biliary tract cancers in a cohort of US veterans. *Br J Cancer*. 1995;72:1556-1558.
27. Moerman CJ, Bueno de Mesquita HB, Smeets FW, Runia S. Lifestyle factors including diet and cancer of the gallbladder and bile duct: a population-based case-control study in the Netherlands. *Eur J Cancer Prev.* 1997;6:139-142.
28. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
29. Oertli D, Herzog U, Tondelli P. Primary carcinoma of the gallbladder: operative experience during a 16 year period. *Eur J Surg*. 1993;159:415-420.
30. Wood R, Fraser LA, Brewster DH, Garden OJ. Epidemiology of gallbladder cancer and trends in cholecystectomy rates in Scotland, 1968-1998. *Eur J Cancer*. 2003;39:2080-2086.
31. Dutta U, Nagi B, Garg PK, Sinha SK, Singh K, Tandon RK. Patients with gallstones develop gallbladder cancer at an earlier age. *Eur J Cancer Prev.* 2005;14:381-385.
32. Espey DK, Wu XC, Swan J, et al. Annual report to the nation on the status of cancer, 1975-2004, featuring cancer in American Indians and Alaska Natives. *Cancer*.2007:2119-2152.
33. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin*. 2001;51:349-364.
34. Itoi T, Watanabe H, Ajioka Y, et al. APC, K-ras codon 12 mutations and p53 gene expression in carcinoma and adenoma of the gall-bladder suggest 2 genetic pathways in gall-bladder carcinogenesis. *Pathol Int*. 1996;46:333-340.