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

Melissa Jim

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

David G. Perdue

University of Minnesota, perdu001@umn.edu

Lisa C. Richardson

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

David K. Espey

Centers for Disease Control and Prevention, david.espey@ihs.gov

John T. Redd

Centers for Disease Control and Prevention

See next page for additional authors

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Jim, Melissa; Perdue, David G.; Richardson, Lisa C.; Espey, David K.; Redd, John T.; Martin, Howard J.; Kwong, Sandy L.; Kelly, Janet J.; Henderson, Jeffrey A.; and Ahmed, Faruque, "Primary Liver Cancer Incidence Among American Indians and Alaska Natives, US, 1999–2004" (2008). *Public Health Resources*. 257.

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Authors

Melissa Jim, David G. Perdue, Lisa C. Richardson, David K. Espey, John T. Redd, Howard J. Martin, Sandy L. Kwong, Janet J. Kelly, Jeffrey A. Henderson, and Faruque Ahmed

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

Supplement to Cancer

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

Melissa A. Jim, MPH^{1,2}
 David G. Perdue, MD, MSPH^{3,4}
 Lisa C. Richardson, MD, MPH¹
 David K. Espey, MD^{1,2}
 John T. Redd, MD, MPH^{2,5}
 Howard J. Martin, PhD⁶
 Sandy L. Kwong, MPH⁷
 Janet J. Kelly, MS, MPH⁸
 Jeffrey A. Henderson, MD, MPH⁹
 Faruque Ahmed, PhD¹⁰

¹ Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia.

² Division of Epidemiology and Disease Prevention, Indian Health Service, Albuquerque, New Mexico.

³ Division of Gastroenterology and Hepatology, Cancer Center, and Program in Health Disparities Research, University of Minnesota, Minneapolis, Minnesota.

⁴ Minnesota Gastroenterology, P.A., Minneapolis, Minnesota.

⁵ Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia.

⁶ Virginia Cancer Registry, Office of Family Health Services, Virginia Department of Health, Richmond, Virginia.

⁷ Cancer Surveillance Section, California Department of Public Health, Sacramento, California.

⁸ Office of Alaska Native Health Research, Alaska Native Epidemiology Center, Alaska Native Tribal Health Consortium, Anchorage, Alaska.

⁹ Black Hills Center for American Indian Health, Rapid City, South Dakota.

¹⁰ National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

BACKGROUND. American Indians and Alaska Natives (AI/AN) experience higher morbidity and mortality from primary liver cancer than other United States (US) populations, but racial misclassification in medical records results in underestimates of disease burden.

METHODS. To reduce misclassification, National Program of Cancer Registries and Surveillance, Epidemiology, and End Results data were linked with Indian Health Service (IHS) enrollment records to compare primary liver cancer incidence and stage at diagnosis between AI/AN and non-Hispanic whites (NHW) living within the regionalized IHS Contract Health Service Delivery Area counties. Incidence rates are expressed per 100,000 persons and age-adjusted by 19 age groups to the 2000 US standard population. **RESULTS.** Overall, AI/AN have a higher proportion of hepatocellular carcinoma compared with NHW, 77.8% versus 66.7%. Liver cancer incidence rates among AI/AN males and females were higher than those among NHW males and females for all regions except for the East. Among males, rates ranged from 7.3 (95% confidence interval [CI], 3.8-12.6) in the East to 17.2 (95% CI, 10.4-26.3) in Alaska. Among females, rates ranged from 3.8 (95% CI, 1.4-8.2) in the East to 6.9 (95% CI, 3.6-11.6) in Alaska. The AI/AN rates for all regions were consistently higher than the NHW rates at every age. An increasing trend among AI/AN was suggested but did not achieve statistical significance.

CONCLUSIONS. Reducing racial misclassification revealed higher disparities in primary liver cancer incidence between NHW and AI/AN populations than previously reported. Further description of the reasons for regional differences in this disparity is needed, as are programs to reduce risk factors and to diagnose primary liver cancer at earlier, more treatable stages. *Cancer* 2008;113(5 sup):1244-55. Published 2008 by the American Cancer Society.*

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.

The authors thank Dr. Brian J. McMahon of the Arctic Investigations Program, Centers for Disease

Control and Prevention, Anchorage, Alaska, for his helpful comments on the manuscript.

Address for reprints: Melissa A. Jim, MPH, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, c/o IHS Division of Epidemiology and Disease Prevention, 5300 Homestead Road NE, Albuquerque, NM 87110; Fax: (505) 248-4393; E-mail: melissa.jim@ihs.gov

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

KEYWORDS: liver cancer, hepatocellular carcinoma, incidence, American Indian, Alaska Native, misclassification, NPCR, SEER, United States, health disparity.

The liver is a common site of metastasis for tumors originating in other organs. In this paper we will focus on cancers that originate in the liver, not on cancers that begin at other sites and metastasize to the liver. Primary liver cancer refers to a heterogeneous group of malignancies that includes hepatocellular carcinomas (HCC), intrahepatic cholangiocarcinomas and, more rarely, angiosarcomas, hemangiosarcomas, and hepatoblastomas. Risk factors for liver cancer vary by histology; those associated with HCC include chronic infection with hepatitis B or C viruses, alcoholic cirrhosis, hemochromatosis, nonalcoholic steatohepatitis (NASH), and primary biliary cirrhosis.¹ Alcohol consumption and possibly tobacco use and diabetes may synergistically increase this risk.²⁻⁸ Primary sclerosing cholangitis and congenital biliary abnormalities are strong risk factors for cholangiocarcinoma in the United States, whereas parasitic biliary infections and recurrent pyogenic cholangitis play a larger role worldwide.⁹⁻¹⁴

American Indians and Alaska Natives (AI/AN) experience higher morbidity and mortality from primary liver cancer than other United States (US) populations.¹⁵⁻¹⁸ During the years 2000 to 2004, primary liver cancer was the 9th leading cause of cancer mortality in US males and the 11th in US females.² It was, however, 4th among AI/AN males and 6th among AI/AN females living in counties served by the Indian Health Service (IHS).¹⁶ In addition, liver cancer mortality rates were 102% higher for AI/AN males and 150% higher for AI/AN females than for all races of males and females during this period. However, AI/AN populations vary greatly in terms of culture, diet, genetics, and known cancer risk factors, and thus important regional differences in cancer incidence may be missed by national summary statistics. For example, from 1990 to 2001, mortality rates from liver cancer among IHS's geographic regions ranged from 5.5 per 100,000 for AI/AN living on the Pacific Coast to 10.6 in the Southwest, all of which were higher than the US all-races rate of 4.6.¹⁷ Regional differences in the incidence of primary liver cancer, however, have not been thoroughly investigated.

Accurate determination of cancer burden is a critical first step toward addressing health disparities. High rates of racial misclassification in medical records and on death certificates make determining cancer incidence and mortality rates for AI/AN populations difficult.^{19,20} Data from the National

Longitudinal Mortality Survey correlating self-identified race from current population surveys with race on death certificates found that AI/AN are classified as another race 44.8% of the time.²¹ Although wide regional and urban/rural variation exists, AI/AN are more likely to be misclassified as another race than are other racial groups, resulting in underestimates of both cancer incidence and mortality.²²⁻²⁵

This study links cancer incidence data from central cancer registries with IHS patient registration databases as 1 way to minimize the effects of racial misclassification.²⁶ Our objective was to compare regional liver cancer incidence rates and stage at diagnosis among AI/AN to those in non-Hispanic whites (NHW) living in the same regions of the United States. Because urban AI/AN are much less likely to access IHS services (and therefore less likely to have racial misclassification corrected through IHS linkage), we focused on those AI/AN living in IHS Contract Health Service Delivery Areas (CHSDA), defined as counties containing or abutting federally recognized AI/AN reservations and tribal lands, for whom the IHS is responsible for medical services.²⁷

MATERIALS AND METHODS

Cancer Cases

We used data from state and regional population-based cancer registries in the US that collect information on newly diagnosed primary cancers. These registries participate in the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC), Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), or both.²⁸⁻³⁰ Primary cancer site and histology data were coded according to the International Classification of Diseases for Oncology (ICD-O) edition in use at the time of diagnosis and are converted to the Third Edition.³¹

For this study, incidence data for cancer of the liver and intrahepatic bile ducts refer to invasive primary cancers (ICD-O-3 site codes C22.0-C22.1); lymphomas originating in the lymphatic tissue of the liver and Kaposi sarcomas are excluded. Incident cancer cases diagnosed during the time period 1999 to 2004 from population-based state cancer registries that provided permission and that met the *United States Cancer Statistics* standard for high-quality data were included in this analysis (see footnote to Table 1 for list of registries).²⁶ Analysis was restricted to microscopically confirmed cases for histology only.

TABLE 1
Liver and Intrahepatic Bile Duct Cancer Incidence by Indian Health Service Region for American Indians/Alaska Natives^a and Non-Hispanic Whites, United States, 1999 to 2004

IHS Region	Sex	CHSDA Counties						All Counties					
		AI/AN Count	AI/AN Rate ^b	95% CI for AI/AN Rate	NHW Rate ^b	Rate Ratio (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 (AI/AN:NHW)	95% CI for Rate Ratio
Northern Plains	Both sexes	79	10.9	8.4-13.7	3.7	2.97 ^c	2.29-3.78	106	8.1	6.4-9.9	4.0	2.01 ^c	1.61-2.48
	Male	56	16.0	11.5-21.4	5.4	2.98 ^c	2.14-4.01	75	12.0	9.0-15.5	6.0	2.01 ^c	1.51-2.61
Alaska ^d	Female	23	6.4	4.0-9.7	2.2	2.89 ^c	1.78-4.39	31	4.7	3.1-6.8	2.4	1.97 ^c	1.30-2.82
	Both sexes	40	11.0	7.7-15.2	5.4	2.02 ^c	1.33-2.99	40	11.0	7.7-15.2	5.4	2.02 ^c	1.33-2.99
Southern Plains	Male	26	17.2	10.4-26.3	8.2	2.09 ^c	1.19-3.46	26	17.2	10.4-26.3	8.2	2.09 ^c	1.19-3.46
	Female	14	6.9	3.6-11.6	2.7	2.51 ^c	1.17-5.04	14	6.9	3.6-11.6	2.7	2.51 ^c	1.17-5.04
Pacific Coast	Both sexes	105	8.1	6.6-9.8	4.3	1.88 ^c	1.51-2.31	125	6.8	5.7-8.2	5.0	1.38 ^c	1.14-1.66
	Male	69	11.1	8.6-14.2	6.1	1.81 ^c	1.38-2.35	84	9.4	7.4-11.7	7.4	1.26	0.99-1.58
East	Female	36	5.1	3.6-7.1	2.8	1.84 ^c	1.26-2.60	41	4.3	3.1-5.9	2.9	1.50 ^c	1.06-2.04
	Both sexes	126	9.2	7.5-11.1	4.5	2.06 ^c	1.68-2.49	174	6.9	5.8-8.1	4.5	1.53 ^c	1.29-1.80
Southwest	Male	89	12.8	10.0-16.2	6.6	1.95 ^c	1.52-2.47	118	9.1	7.4-11.1	6.7	1.35 ^c	1.09-1.66
	Female	37	5.8	4.0-8.1	2.6	2.24 ^c	1.54-3.13	56	4.7	3.5-6.2	2.6	1.85 ^c	1.37-2.44
Total	Both sexes	20	5.7	3.4-9.0	4.4	1.29	0.76-2.03	69	2.8	2.1-3.6	4.3	0.65 ^c	0.49-0.83
	Male	14	7.3	3.8-12.6	6.8	1.06	0.56-1.85	53	4.3	3.1-5.8	6.7	0.65 ^c	0.47-0.87
Total	Female	6	3.8	1.4-8.2	2.5	1.55	0.55-3.32	16	1.4	0.8-2.2	2.4	0.58 ^c	0.32-0.94
	Both sexes	159	9.0	7.6-10.5	4.2	2.15 ^c	1.80-2.54	167	8.4	7.1-9.8	3.8	2.20 ^c	1.85-2.59
Total	Male	101	12.2	9.8-15.1	6.3	1.95 ^c	1.55-2.42	108	11.5	9.3-14.1	5.6	2.05 ^c	1.64-2.52
	Female	58	6.3	4.7-8.1	2.3	2.71 ^c	2.01-3.57	59	5.7	4.3-7.4	2.2	2.60 ^c	1.94-3.40
Total	Both sexes	529	9.0	8.2-9.9	4.3	2.11 ^c	1.92-2.32	681	6.5	6.0-7.1	4.3	1.52 ^c	1.40-1.64
	Male	355	12.7	11.3-14.2	6.3	2.00 ^c	1.78-2.25	464	9.2	8.3-10.2	6.6	1.41 ^c	1.27-1.56
Total	Female	174	5.8	5.0-6.8	2.5	2.36 ^c	2.00-2.75	217	4.2	3.6-4.8	2.4	1.71 ^c	1.48-1.96

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

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

^a AI/AN race is reported by NPCR and SEER registries or through linkage with the IHS patient registration database. AI/AN persons of Hispanic origin are included.

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

^c 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.

Years of data and registries used: 1999 to 2004 (41 states and the District of Columbia); Alaska, * Alabama, * Arkansas, Arizona, * California, * Colorado, * Connecticut, * the District of Columbia, Delaware, Florida, * Georgia, Hawaii, Iowa, * Idaho, * Illinois, Indiana, * Kentucky, Louisiana, * Massachusetts, * Maine, * Michigan, * Minnesota, * Missouri, Montana, * North Carolina, * Nebraska, * New Hampshire, New Jersey, New Mexico, * Nevada, * New York, * Ohio, Oklahoma, * Oregon, * Pennsylvania, * Rhode Island, * Texas, * Utah, * Washington, * Wisconsin, * West Virginia, and Wyoming*; 1999 and 2002 to 2004: North Dakota*; 2001 to 2004: South Dakota*; 2003 to 2004: Mississippi* and Virginia; 2004: Tennessee*. *States with at least one county designated as CHSDA. Percentage regional coverage of AI/AN in CHSDA counties to AI/AN in all counties: Alaska = 100%; East = 13.1%; Northern Plains = 59.0%; Southern Plains = 64.1%; Pacific Coast = 55.6%; Southwest = 87.5%.

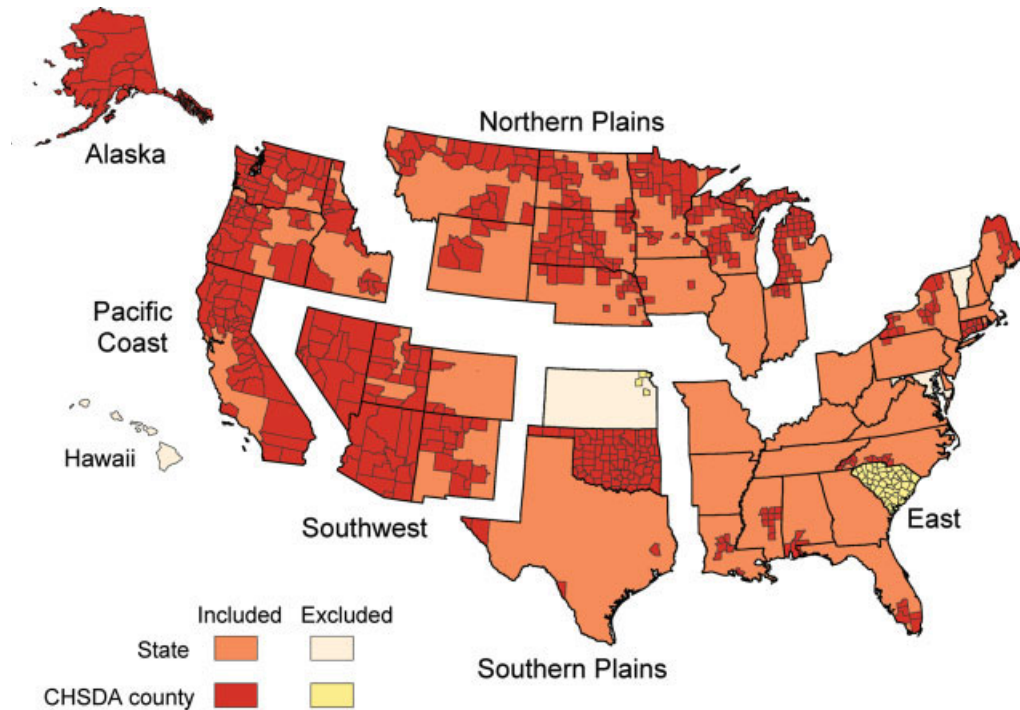


FIGURE 1. States and Contract Health Service Delivery Area (CHSDA) counties by Indian Health Service region are shown.

Cancer cases diagnosed during 2001 to 2003 were staged by use of the 2000 SEER summary staging system.³² Collaborative stage data, first reported for 2004, were not available for analysis. Because of the small number of AI/AN cases, the analyses will include all primary liver cancers, rather than being restricted to hepatocellular carcinoma.

To reduce the misclassification of AI/AN cases as non-Native, all case records from the NPCR and SEER population-based registries were linked with the IHS patient registration database. Files were prepared by the registries and sent to the IHS Division of Epidemiology and Disease Prevention in Albuquerque, New Mexico for linkage. The IHS provides medical services to AI/AN persons who are eligible members of federally recognized tribes. Linkages applied to key patient identifiers were conducted by use of LinkPlus,³³ a probabilistic linkage software program developed by CDC.²⁶

The proportion of AI/AN in the total population is higher in CHSDA counties than in non-CHSDA counties, and data indicate that there is less racial misclassification for AI/AN in these counties than in non-CHSDA counties.³⁴ AI/AN in these counties are also more likely to access IHS services and therefore to have any racial misclassification corrected by our linkage strategy. Analyses were restricted to persons who reside in CHSDA counties unless otherwise noted (Table 1). About 56% of the US AI/AN popula-

tion reside in CHSDA counties. This proportion varies by IHS region: Alaska = 100%; East = 13.1%; Northern Plains = 59.0%; Southern Plains = 64.1%; Pacific Coast = 55.6%; Southwest = 87.5%. Details of the IHS regions (Alaska, Pacific Coast, Northern Plains, Southern Plains, Southwest, and East) and CHSDA areas are provided elsewhere²⁶ and shown in Figure 1.

Population Estimates

County-level population estimates produced by the US Census Bureau were used as denominators in the rate calculations. To manage multiple race data collected since 2000, a technique of bridging race categories into single-race annual population estimates was developed by the CDC's National Center for Health Statistics in collaboration with the Census Bureau.³⁵ The NCI makes further refinements regarding race and county geographic codes and provides public access to these estimates at the SEER Website.³⁶

Statistical Analyses

Two sets of statistics are provided for AI/AN and NHW populations: 1) data from all counties in all states that meet cancer registry data quality criteria (referred to as "All Counties"), and 2) data from CHSDA counties in all states that meet quality criteria. In addition, All-Counties data and CHSDA counties data are provided for each IHS region. The

TABLE 2
Invasive Liver and Intrahepatic Bile Duct Cancer Percentage Histology Distribution Among Microscopically Confirmed Cases by Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites, CHSDA Counties, United States, 1999 to 2004

IHS Region	Adenocarcinoma, NOS ^a		Cholangiocarcinoma ^b		Combined Hepatocellular and Cholangiocarcinoma ^c		Hepatocellular Carcinoma ^d		Other Adenocarcinomas ^e		Other Malignant Histologies	
	AI/AN, % ^f	NHW, % ^f	AI/AN, % ^f	NHW, % ^f	AI/AN, % ^f	NHW, % ^f	AI/AN, % ^f	NHW, % ^f	AI/AN, % ^f	NHW, % ^f	AI/AN, % ^f	NHW, % ^f
	Northern Plains	1.3	11.5	11.4	16.1	3.4	1.4	73.6	59.9	6.1	2.9	4.3
Alaska	~	8.0	6.8	12.2	~	4.1	70.7	64.5	14.7	1.5	7.7	9.7
Southern Plains	6.4	13.8	3.7	11.1	1.8	0.7	79.8	56.1	2.3	5.2	5.8	13.1
Pacific Coast	2.3	6.3	9.0	13.6	1.5	0.7	81.6	68.1	~	3.7	5.8	7.3
East	~	5.8	~	13.1	~	1.7	74.5	69.2	12.5	2.3	13.0	7.8
Southwest	6.1	7.2	7.6	11.0	~	1.0	76.6	70.3	3.3	3.1	6.5	6.9
Total	3.7	7.5	7.1	13.4	1.2	1.0	77.8	66.7	3.9	3.3	6.2	8.2

Source: Cancer registries in the National Program of Cancer Registries of the Centers for Disease Control and Prevention and the Surveillance, Epidemiology, and End Results program of the National Cancer Institute; see Table 1 for states included.

CHSDA indicates Contract Health Service Delivery Areas; NOS, not otherwise specified; IHS, Indian Health Service; AI/AN: American Indians/Alaska Natives; NHW: non-Hispanic whites.

^a Includes histology 8140.

^b Includes histology 8160.

^c Includes histology 8180.

^d Includes histologies 8170 to 8175.

^e Includes histologies 8141 to 8159, 8161 to 8169, 8176 to 8179, 8181 to 8389, 8401, 8408, 8410, 8411, 8413, 8441, 8450, 8460, 8470, 8480 to 8482, 8490, 8500, 8503, 8504, 8510, 8520, 8525, 8530, 8571 to 8574, 8576, 8650, 9070, 9110.

^f Percentages in the histology distribution are age-adjusted to the 2000 US standard population and may not add to 100.0% due to rounding.

~ If no cases were reported, then percentage distributions could not be calculated.

results described in the text refer to persons who reside in CHSDA counties, unless otherwise noted. Additional information about cases and population coverage is available elsewhere.²⁶

For all AI/AN and NHW populations, cancer incidence rates are expressed per 100,000 persons and are age-adjusted by 19 age groups (<1, 1-4, 5-9, . . . , 80-84, ≥85) to the 2000 US standard population by use of the direct method.²⁸ Percent distributions are also age-adjusted.³⁷ Rate ratios with 95% confidence intervals (CI) are provided for regional comparisons of incidence rates between AI/AN and NHW populations (Table 1). Rate ratios are calculated as the age-adjusted incidence among AI/AN persons divided by the age-adjusted incidence among NHW persons. For all analyses, case counts are suppressed when the category of interest contains <6 cases. Annual percent change (APC) was used to describe fixed interval trends from 1999 to 2004. Incidence rates, rate ratios, APC, and 95% modified gamma CI (95% CI)³⁸ are generated by use of SEER*Stat Software, Version 6.3.6.³⁹

RESULTS

Cancer Incidence

From 1999 to 2004, there were 681 cases of liver cancer diagnosed in AI/AN in all regions (Table 1) and 54,317 cases diagnosed in NHW in all regions. When the analysis was restricted to CHSDA counties, there

were 529 cases of liver cancer diagnosed in AI/AN (Table 1) and 11,805 cases diagnosed in NHW. Only 63.7% of the 529 AI/AN cases and 71.2% of the 11,805 NHW cases were microscopically confirmed. Microscopically confirmed cancers among AI/AN cases were 77.8% hepatocellular carcinoma, 7.1% cholangiocarcinoma, 6.2% other malignant histologies, 3.9% other adenocarcinomas, 3.7% adenocarcinoma not otherwise specified, and 1.2% combined hepatocellular and cholangiocarcinoma (Table 2). The microscopically confirmed cases among NHW were 66.7%, 13.4%, 8.2%, 3.3%, 7.5%, and 1.0%, respectively. The higher proportion of HCC among AI/AN compared with NHW was consistent when the analysis was repeated using all cases, with the exception of the East. Because of the small number of AI/AN cases, the analyses will include all primary liver cancers, rather than being restricted to hepatocellular carcinoma.

Of the 681 cases of liver cancer diagnosed among AI/AN, 77.7% of all incident cases were diagnosed among AI/AN residents of CHSDA counties (Table 1). Liver cancer incidence rates for AI/AN populations residing in CHSDA counties were uniformly higher than rates based on AI/AN residents in All Counties, with the exception of Alaska, where all counties are designated as CHSDA counties. In contrast, there was very little difference in NHW rates between CHSDA counties and All Counties. These findings are

TABLE 3
Invasive Liver and Intrahepatic Bile Duct Cancer Incidence Rates and Percentage Distribution by Age and Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites, CHSDA Counties, United States, 1999 to 2004

IHS Region	<45 Years				45-59 Years				60-74 Years				75+ Years			
	Count	% of Cases ^a	Rate ^b	95% CI	Count	% of Cases ^a	Rate ^b	95% CI	Count	% of Cases ^a	Rate ^b	95% CI	Count	% of Cases ^a	Rate ^b	95% CI
American Indian/Alaska Native																
Northern Plains	7	8.9	0.7	0.3-1.4	30	38.0	15.6 ^c	10.5-22.3	25	31.6	33.7 ^c	21.6-50.0	17	21.5	66.6 ^c	38.7-106.9
Alaska	~	10.0	0.9	0.2-2.3	12	30.0	12.8	6.6-22.4	12	30.0	28.4	14.6-49.9	12	30.0	84.8 ^c	43.6-149.1
Southern Plains	~	4.8	0.5	0.1-1.0	32	30.5	10.7 ^c	7.3-15.1	41	39.0	29.2 ^c	20.9-39.7	27	25.7	45.4 ^c	29.9-66.2
Pacific Coast	9	7.1	0.6	0.3-1.2	59	46.8	16.3 ^c	12.4-21.0	36	28.6	27.2 ^c	18.9-37.8	22	17.5	48.4 ^c	30.3-73.5
East	~	10.0	0.6	0.1-2.2	10	50.0	12.0	5.8-22.1	~	15.0	7.7	1.6-23.7	~	25.0	38.3	12.4-89.3
Southwest	16	10.1	0.8	0.4-1.2	50	31.4	12.0 ^c	8.9-15.8	52	32.7	27.2 ^c	20.2-35.7	41	25.8	56.8 ^c	40.8-77.1
Total	43	8.1	0.7	0.5-0.9	193	36.5	13.4 ^c	11.5-15.4	169	31.9	27.4 ^c	23.4-31.9	124	23.4	54.1 ^c	45.0-64.5
Non-Hispanic white																
Northern Plains	96	5.1	0.3	0.3-0.4	429	22.9	4.6	4.2-5.1	680	36.2	12.9	12.0-13.9	672	35.8	20.4	18.9-22.0
Alaska	14	12.0	0.8	0.4-1.3	52	44.4	8.6	6.4-11.2	35	29.9	18.3	12.6-25.6	16	13.7	24.3	13.8-39.7
Southern Plains	36	4.2	0.4	0.3-0.5	193	22.6	5.6	4.8-6.4	303	35.4	13.9	12.4-15.5	323	37.8	26.1	23.3-29.1
Pacific Coast	213	5.1	0.4	0.4-0.5	1312	31.2	7.4	7.0-7.8	1339	31.8	14.2	13.5-15.0	1346	32.0	22.2	21.0-23.4
East	133	4.5	0.4	0.3-0.5	666	22.5	5.9	5.4-6.4	1082	36.6	15.9	15.0-16.9	1077	36.4	23.4	22.0-24.8
Southwest	91	5.1	0.4	0.4-0.5	490	27.4	6.6	6.1-7.2	691	38.6	14.2	13.2-15.3	516	28.9	19.7	18.1-21.5
Total	583	4.9	0.4	0.4-0.4	3142	26.6	6.3	6.1-6.5	4130	35.0	14.4	14.0-14.8	3950	33.5	22.1	21.4-22.8

Source: Cancer registries in the National Program of Cancer Registries of the Centers for Disease Control and Prevention and the Surveillance, Epidemiology, and End Results program of the National Cancer Institute; see Table 1 for states included.

CHSDA indicates Contract Health Service Delivery Areas; IHS, Indian Health Service; CI, confidence interval.

^a Percentages may not add to 100.0% due to rounding.

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

^c AI/AN rate is statistically significantly higher than the NHW rate ($P < .05$).

~ Counts less than 6 are suppressed; if no cases were reported, then row percentages and rates could not be calculated.

consistent with improved classification of AI/AN cancer cases within CHSDA counties; the improvement resulted in increased rates for AI/AN, but it had minimal effect on NHW rates.

Age-adjusted liver cancer incidence rates (expressed per 100,000) for AI/AN and NHW persons, stratified by region, sex, and CHSDA county, are shown in Table 1. Liver cancer incidence rates among AI/AN males were statistically significantly higher than those among NHW males for all regions except for the East. Rates ranged from 7.3 (95% CI, 3.8-12.6) in the East to 17.2 (95% CI, 10.4-26.3) in Alaska. In contrast, there was relatively little regional variation in rates for NHW males, which ranged from 5.4 in the Northern Plains to 8.2 in Alaska.

Like the rates for males, rates per 100,000 among AI/AN females were statistically significantly higher than those among NHW females for all regions, except for the East. Rates per 100,000 ranged from 3.8 (95% CI, 1.4-8.2) in the East to 6.9 (95% CI, 3.6-11.6) in Alaska. In contrast, there was relatively little regional variation in rates for NHW females, which ranged from 2.2 in the Northern Plains to 2.8 in the Southern Plains.

Age-adjusted liver cancer incidence rates stratified by region and age are shown in Table 3. The AI/AN rates for all regions were consistently higher than the NHW rates at every age. The rates in the 45 to 59, 60 to 74, and 75+ age groups were statistically significantly higher than the NHW rates in the Northern Plains, Southern Plains, Pacific Coast, Southwest, and All Regions. In Alaska, only the rates in the 75+ age group were statistically significantly higher than the NHW rates. Differences between AI/AN and NHW were not statistically significant in the East and among the <75 age groups in Alaska.

Cancer Stage

Age-adjusted liver cancer incidence rates in CHSDA counties, stratified by region and stage, are shown in Table 4. Age-adjusted percent distributions show AI/AN persons were less likely than NHW to be diagnosed with localized (24.7% vs 28.6%) or distant (13.5% vs 16.7%) liver cancer. AI/AN were more likely than NHW to be diagnosed with regional or unstaged cancer. Exceptions were found in the Alaska and Pacific Coast regions, where over 30% of AI/AN were diagnosed in the localized stage. These 2 regions also

TABLE 4
Invasive Liver and Intrahepatic Bile Duct Cancer Incidence Rates and Percentage Distribution by Stage^a and Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites, CHSDA Counties, United States, 2001 to 2003

IHS Region	Localized			Regional			Distant			Unstaged			All							
	Count	Rate ^b	% of Cases ^c	Count	Rate ^b	% of Cases ^c	Count	Rate ^b	% of Cases ^c	Count	Rate ^b	% of Cases ^c	Count	Rate ^b	% of Cases ^c					
American Indian/Alaska Native																				
Northern Plains	8	1.8	0.7-3.8	14	3.4	1.8-5.7	30.4	~	0.9	0.2-2.4	8.0	19	5.2	2.9-8.2	46.4	11.2	7.9-15.3	100		
Alaska	7	3.5	1.3-7.3	~	1.5	0.3-4.5	13.3	6	3.3	1.1-7.2	29.2	~	2.9	0.7-7.1	25.7	20	11.3	6.6-17.6	100	
Southern Plains	14	1.9	1.0-3.2	24.4	10	1.5	0.7-2.8	19.2	10	1.4	0.7-2.6	17.9	19	2.9	1.7-4.5	37.2	53	7.8	5.8-10.2	100
Pacific Coast	22	2.6	1.6-4.0	32.1	17	2.3	1.3-3.8	28.4	8	0.9	0.4-1.8	11.1	15	2.4	1.3-4.0	29.6	62	8.1	6.1-10.6	100
East	~	1.4	0.3-4.3	16.3	~	1.4	0.1-4.7	16.3	~	0.4	0.0-2.7	4.7	8	5.3	2.2-10.5	61.6	14	8.6	4.5-14.6	100
Southwest	21	2.2	1.3-3.3	24.7	22	2.2	1.4-3.4	24.7	10	1.0	0.5-1.8	11.2	31	3.5	2.3-5.0	39.3	84	8.9	7.0-11.1	100
Total	75	2.2	1.7-2.8	24.7	68	2.2	1.7-2.8	24.7	38	1.2	0.8-1.6	13.5	96	3.4	2.7-4.2	38.2	277	8.9	7.9-10.1	100
Non-Hispanic white																				
Northern Plains	248	1.0	0.8-1.1	26.3	194	0.7	0.6-0.9	18.4	160	0.6	0.5-0.7	15.8	398	1.5	1.4-1.7	39.5	1000	3.8	3.6-4.1	100
Alaska	16	1.2	0.7-2.1	23.5	12	1.0	0.5-1.9	19.6	6	0.4	0.1-0.9	7.8	25	2.4	1.5-3.8	47.1	59	5.1	3.7-6.8	100
Southern Plains	104	1.1	0.9-1.3	27.5	62	0.6	0.5-0.8	15.0	84	0.8	0.7-1.0	20.0	155	1.5	1.3-1.8	37.5	405	4.0	3.7-4.5	100
Pacific Coast	688	1.4	1.3-1.6	31.8	524	1.1	1.0-1.2	25.0	363	0.8	0.7-0.9	18.2	537	1.1	1.0-1.2	25.0	2112	4.4	4.2-4.6	100
East	431	1.3	1.2-1.4	30.2	261	0.8	0.7-0.9	18.6	227	0.7	0.6-0.8	16.3	519	1.5	1.4-1.7	34.9	1438	4.3	4.1-4.5	100
Southwest	229	1.1	0.9-1.2	26.8	134	0.6	0.5-0.7	14.6	123	0.6	0.5-0.7	14.6	399	1.8	1.6-2.0	43.9	885	4.1	3.8-4.4	100
Total	1716	1.2	1.2-1.3	28.6	1187	0.9	0.8-0.9	21.4	963	0.7	0.7-0.7	16.7	2033	1.4	1.4-1.5	33.3	5899	4.2	4.1-4.3	100

Source: Cancer registries in the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention and the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute; see Table 1 for states included. CHSDA indicates Contract Health Service Delivery Areas; IHS, Indian Health Service; CI, confidence interval.

^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 Percentage stage distribution is age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).

~ Counts of less than 6 are suppressed; if no cases were reported, then rates and age-adjusted percentage distributions could not be calculated.

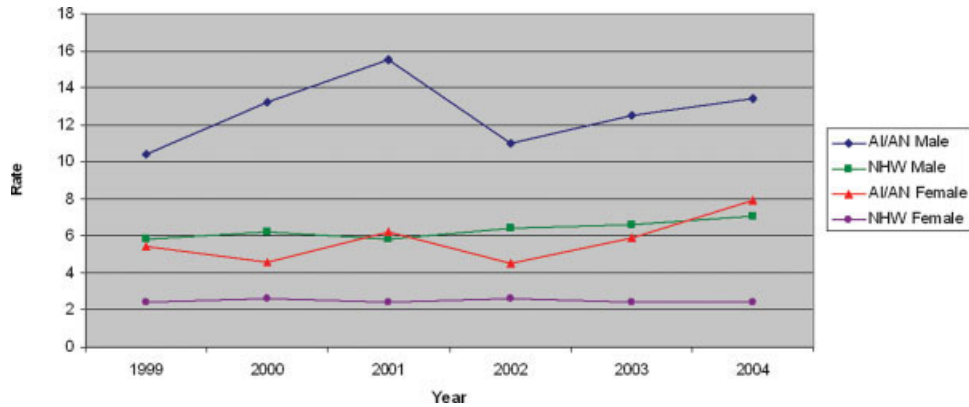


FIGURE 2. Liver cancer incidence rates for American Indians/Alaska Natives (AI/AN) and non-Hispanic whites NHW. Source: Cancer registries in National Program of Cancer Registries of the Centers for Disease Control and Prevention and/or the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. See Table 1 for states included. Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).

TABLE 5
Invasive Liver and Intrahepatic Bile Duct Cancer Incidence Annual Percentage Change by Year and Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites, CHSDA Counties, United States, 1999 to 2004

IHS Region	Both Sexes		Male		Female	
	AI/AN APC ^a	NHW APC ^a	AI/AN APC ^a	NHW APC ^a	AI/AN APC ^a	NHW APC ^a
Northern Plains	8.9	1.3	2.5	2.6	23.8	-2.2
Alaska	15.2	-3.6	31.0	-6.7	~	-0.2
Southern Plains	7.4	0.8	3.0	1.7	12.2 ^b	-1.1
Pacific Coast	-2.1	4.1 ^b	-2.8	5.0 ^b	-2.8	1.4
East	7.9	2.4	~	4.0	~	-2.0
Southwest	0.4	2.9	-5.9	3.7	7.3	-0.1
Total	4.0	2.6 ^b	1.4	3.8 ^b	8.2	-0.6

Source: Cancer registries in the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention and the Surveillance, Epidemiology, and End Results program of the National Cancer Institute; see Table 1 for states included.

CHSDA indicates Contract Health Service Delivery Areas; IHS, Indian Health Service; AI/AN, American Indians/Alaska Natives; APC, annual percentage change; NHW, non-Hispanic whites.

^a Percentage changes were calculated using 2 years for each end point; APCs were calculated by using the weighted least-squares method.

^b APC is significantly different from zero ($P < .05$).

~ Statistic could not be calculated.

were less likely to have unstaged liver cancer. A large percentage of cases diagnosed in CHSDA counties were unstaged for both AI/AN and NHW (38.2% and 33.3%, respectively).

Trends

Finally, because recent studies showed increases in liver cancer incidence rates and differences in sex,^{16,40} incidence rates were examined for AI/AN and NHW males and females to assess possible trends (Fig. 2, Table 5). Consistent with published reports, rates of liver cancer varied by sex (Fig. 2). Rates of liver cancer among NHW males significantly

increased by 3.8% per year in all regions, whereas the rates among NHW females decreased slightly by -0.6% per year (Table 5). In contrast, trends for the smaller AI/AN populations varied considerably by region. The incidence rates among AI/AN males increased by 1.4% for all regions and varied from -5.9% in the Southwest to 31.0% in Alaska; however, none of these changes achieved statistical significance. The rates among AI/AN females showed an increase of 8.2% for all regions and varied from -2.8% in the Pacific Coast to 23.8% in the Northern Plains; however, the trend among AI/AN females in the Southern Plains (12.2%) did achieve statistical significance. There was very little difference in the

rates when the analysis was repeated by excluding 5 states that did not have all 6 years of data.

DISCUSSION

By using data from population-based central cancer registries linked with IHS patient registration records and restricting data analysis to CHSDA counties, we found that AI/AN have a higher incidence of primary liver cancer than previously reported.^{28,41} Our finding of higher rates is likely attributable to prior racial misclassification of AI/AN as other races, the net result of which is an underestimation of actual disease risk.¹⁷ We also found that both AI/AN and NHW males experienced higher incidence rates of primary liver cancer than AI/AN and NHW females, respectively.

Primary liver cancer incidence has been increasing in the general population at the rate of 3.5% per year in males and 1.6% per year in females from 1995 through 2004.¹⁶ Individuals with cirrhosis and chronic liver disease are at higher risk of liver cancer, and the main preventable causes of these conditions are chronic infection with hepatitis B and C viruses, chronic alcohol abuse, and nonalcoholic fatty liver disease.^{16,42}

The development of cirrhosis is a necessary precursor for HCC associated with hepatitis C. Chronic hepatitis C infection confers an approximately 20% increased risk of cirrhosis.⁴³⁻⁴⁷ Incidence rates based on reported cases in 2001 indicate that the AI/AN hepatitis C rate is more than 6 times greater than the hepatitis C rate in NHW.⁴⁸ The risk of developing HCC among cirrhotic hepatitis C patients is approximately 1% to 4% per year worldwide.⁴⁵ With an estimated 4.1 million Americans (1.6%) infected with hepatitis C,⁴³ rates of liver cancer and other complications of hepatitis C are expected to climb over the next 20 years.^{49,50}

Elevated liver cancer rates are part of a large overall disparity in the impact of chronic liver disease (CLD) on AI/AN populations.¹⁸ A nationwide population-based study found that mortality rates from CLD/cirrhosis were twice as high among urban AI/AN than for the general population.⁵¹ The age-specific CLD death rate in AI/AN was over twice as high as in US whites and blacks, and over 3 times as high as in Asian/Pacific Islanders.¹⁸ Although rates observed in other racial groups decreased, the age-adjusted death rates from CLD increased among AI/AN from 1990 to 1998.¹⁸ Several reasons have been proposed to explain the disparity in AI/AN liver cancer rates compared with other populations.

Cirrhosis in itself, regardless of the cause, is a risk factor for primary liver cancer, and the most common cause of cirrhosis in the US is alcoholic

liver disease.⁵² Alcohol-related morbidity varies across AI/AN communities, but it remains a significant health concern for many tribal groups.⁵³ Alcohol abuse and hepatitis B and C synergistically increase liver cancer risk^{6,7} and are likely contributors to disparities between AI/AN and NHW.

A recent IHS/CDC study found that more than half of prevalent cases of CLD had alcohol-related liver disease or hepatitis C, or both.⁵⁴ Self-reported use of alcohol has been collected by the Behavioral Risk Factor Surveillance Survey (BRFSS) since 1984.⁵⁵ The most recent BRFSS data show prevalence rates of heavy drinking (defined as more than 2 drinks per day within the past 30 days for males and more than 1 drink per day within the past 30 days for females) prevalence rates were similar for NHW and AI/AN, but the data show that binge drinking (defined as 5 or more drinks on 1 occasion within the past 30 days) is more prevalent in AI/AN.⁵⁶ Although the rates of heavy drinking are similar in the 2 populations, interactions between chronic hepatitis infections and heavy alcohol use may cause higher rates of cirrhosis, thereby leading to higher rates of HCC in AI/AN.^{57,58} The higher rates of primary liver cancer that we observed in AI/AN males relative to AI/AN females may be at least partially explained by higher prevalence in AI/AN males than in AI/AN females of both hepatitis C-related and alcohol-related chronic liver disease.⁵⁴

Other diseases implicated in the development of cirrhosis and subsequent HCC risk may also disproportionately affect AI/AN populations. Primary biliary cirrhosis (PBC) has been implicated as a cause of chronic liver disease among Canadian First Nation peoples in British Columbia.^{59,60} Among indications for liver transplant in British Columbia from 1989 to 1998, 25% of persons requiring a transplant for PBC were of First Nations descent, although persons of First Nations descent comprise only 4% of the British Columbia population.⁶⁰ Thus, there is evidence that PBC may be more common in AI/AN populations than in NHW populations, and that PBC may therefore contribute to the elevated primary liver cancer rates we present. A population-based study from Alaska reported higher rates of autoimmune hepatitis among Alaska Natives than in a Norwegian population,^{61,62} although the prevalence of autoimmune hepatitis is unknown in AI/AN in the continental US.

Before the introduction of the hepatitis B vaccine, hepatitis B was endemic among AI/AN in Alaska.⁶³⁻⁶⁵ However, routine screening and infant vaccination programs begun in the early 1980s have drastically reduced hepatitis B incidence in this region.⁶³ Unfortunately, little is known about the

prevalence of chronic viral hepatitis in AI/AN populations outside of Alaska. Our study illustrates the need for a better understanding of the relative contributions of hepatitis C, hepatitis B, and alcohol abuse to elevated liver cancer rates in AI/AN.

Diabetes and obesity prevalence may also be partially responsible for primary liver cancer disparities in AI/AN. Diabetes and obesity have both been identified as emerging risk factors for HCC because of their being risk factors for NASH.^{66,67} NASH can result in cirrhosis, and it is thought to be responsible for a significant proportion of cryptogenic cirrhosis and HCC.^{68,69} AI/AN in all regions have a higher prevalence of obesity than NHW and AI/AN have an elevated prevalence of diabetes.^{56,70,71} It is likely that NASH plays a significant role in the development of HCC in AI/AN.

Cigarette smoking has also been implicated as an etiologic agent in the development of multiple cancers, including HCC,⁷² and evidence suggests a synergistic effect between tobacco use, alcohol consumption, and obesity in HCC's development.³ AI/AN populations have the highest smoking rates in the country.^{56,70,73} During the most recent BRFSS reporting period (2000-2006),⁵⁶ 31.1% of AI/AN participants reported currently being habitual smokers, compared with 22.8% of NHW participants. AI/AN in the Southwest reported lower smoking rates than AI/AN in other regions (21.1%), whereas rates were 40.2% in the Northern Plains and 40.0% in Alaska. AI/AN males were more likely to smoke than AI/AN females except in the Southern Plains, where current smoking rates were nearly the same. The use of tobacco for traditional purposes in many AI/AN communities calls for culturally sensitive and specific cessation programs.

Several limitations need to be considered when interpreting the results in this report. 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 eligible for IHS services, or who have not accessed IHS health services. Many AI/AN who live primarily in urban non-CHSDA areas are under represented, and thus the findings are not necessarily generalizable to all AI/AN in the US or in individual IHS regions.²⁶ Because of the small number of AI/AN cases, we were not able to restrict our analyses to HCC only, which comprised 77.8% of our microscopically confirmed cases.

In summary, AI/AN in all regions experienced higher primary liver cancer incidence than NHW.

According to BRFSS data, there is a higher burden of risk factors associated with primary liver cancer—including diabetes, obesity, cigarette smoking, and heavy alcohol use—in AI/AN than in NHW. These factors may contribute to the higher incidence of primary liver cancer in AI/AN communities. Furthermore, there are likely complex interactions of etiologic factors yet to be discovered. Data on several of the most important risk factors for primary liver cancer, such as the prevalence of chronic hepatitis B and C virus infection among AI/AN populations, are needed.

The high prevalence of known risk factors for primary liver cancer among AI/AN populations will make this group of cancers an important health concern for the foreseeable future. Clinical care of AI/AN individuals should include vaccination against hepatitis B, behavioral risk screening for alcohol abuse and hepatitis B and C risk factors such as intravenous drug use and sexually transmitted infections, as well as the development of culturally specific weight management, diabetes, and nontraditional tobacco cessation programs. Periodic screening with alpha-fetoprotein or by alpha-fetoprotein and ultrasound among patients with a high prevalence of known risk factors has been recommended to detect HCC tumors at earlier stages; however, it is unclear whether this screening improves disease-specific or all-cause mortality.⁷⁴ Given the higher incidence of primary liver cancer in AI/AN communities, more work is needed to determine the potential impact of programmatic screening in this population.⁷⁵

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