9-1-2008

Gastric Cancer Among American Indians and Alaska Natives in the United States, 1999–2004

Charles Wiggins
University of New Mexico, cwiggins@salud.unm.edu

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

Jeffrey A. Henderson
Black Hills Center for American Indian Health

Michael G. Bruce
Centers for Disease Control and Prevention

Anne P. Lanier
Alaska Native Tribal Health Consortium, aplanier@anthc.org

See next page for additional authors

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

Supplement to ***Cancer***

Gastric Cancer Among American Indians and Alaska Natives in the United States, 1999–2004

Charles L. Wiggins, PhD, MSPH[1]
David G. Perdue, MD, MSPH[2,3]
Jeffrey A. Henderson, MD, MPH[4]
Michael G. Bruce, MD, MPH[5]
Anne P. Lanier, MD, MPH[6]
Janet J. Kelley, MS, MPH[6]
Brenda F. Seals, PhD, MPH[7]
David K. Espey, MD[8]

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

[2] Division of Gastroenterology and Hepatology, University of Minnesota Cancer Center, Minneapolis, Minnesota.

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

[4] Black Hills Center for American Indian Health, Rapid City, South Dakota.

[5] Arctic Investigations Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska.

[6] Alaska Native Epidemiology Center, Alaska Native Tribal Health Consortium, Anchorage, Alaska.

[7] Native American Cancer Research, Pine, Colorado.

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

Supported by Contract N01-PC-35138 from the National Cancer Institute and by the University of New Mexico Cancer Research and Treatment Center and by the University of New Mexico Cancer Center, a recipient of NCI Cancer Support Grant P30-CA118100

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 and Prevention.

BACKGROUND. Gastric cancer incidence rates for American Indians and Alaska Natives (AI/ANs) historically have exceeded those for non-Hispanic whites (NHWs). Previous reports may have underestimated the true burden of gastric cancer in AI/AN populations because of misclassification of AI/AN race in cancer registries.

METHODS. Population-based cancer registry data from 1999 through 2004 were used to describe gastric cancer incidence in AI/ANs and NHWs in the US. To address misclassification of race, registry data were linked with Indian Health Service administrative records, and analyses were restricted to residents of Contract Health Service Delivery Areas (CHSDA). Disease patterns were assessed for 6 geographic regions and for all regions combined. Rates were expressed per 100,000 population and were age-adjusted to the 2000 US standard population.

RESULTS. In CHSDA counties, gastric cancer incidence rates for AI/ANs were higher than the rates for NHWs across most regions. For both sexes combined, AI/AN rates ranged from 6.1 in the East region to 24.5 in Alaska; there was relatively little regional variation in NHW rates. Most patients with gastric cancer were diagnosed with late-stage disease, regardless of race, age, or sex. In some regions, cancer rates in the central/distal portions of the stomach were higher among AI/ANs than among NHWs, whereas rates in the proximal stomach were similar between the 2 populations.

CONCLUSIONS. AI/ANs are generally at greater risk for gastric cancer than NHWs. Relatively high rates of cancer in the central/distal portions of the stomach among AI/ANs in some geographic regions may indicate a disproportional burden of *Helicobacter pylori*-associated disease. ***Cancer*** **2008;113(5 suppl):1225–33.** *Published 2008 by the American Cancer Society.**

KEYWORDS: cancer, incidence, American Indian, Alaska Native, misclassification, National Program of Cancer Registries, Surveillance, Epidemiology, and End Results, US, health disparity, gastric, stomach.

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.

Address for reprints: Charles Wiggins, PhD, New Mexico Tumor Registry, MSC-11 6020, 1 University of New Mexico, Albuquerque, NM 87131-0001; Fax: (505) 272-3750; E-mail: cwiggins@salud.unm.edu

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

Published 2008 by the American Cancer Society*
DOI 10.1002/cncr.23732
Published online 20 August 2008 in Wiley InterScience (www.interscience.wiley.com).

There is wide geographic variation in the occurrence of gastric cancer.[1-3] Economically developing countries generally have higher incidence and mortality rates of the disease than developed countries,[3] with the notable exceptions of Japan and Korea. Gastric cancer claims an estimated 857,000 lives each year worldwide and is second only to hepatocellular carcinoma as a leading cancer cause of death.[1-3]

For reasons that are not understood fully, gastric cancer incidence and mortality rates declined in many countries over the course of the 20th century.[4] Possible reasons that have been hypothesized to explain the decline have included increased fruit and vegetable consumption, decreased intake of foods preserved with salt or by smoking, declines in salt intake, widespread availability of refrigeration, and the reduced prevalence of *Helicobacter pylori* infection. In the US, gastric cancer mortality rates per 100,000 among males declined from 46.3 in 1930 to 5.9 in 2004, and the rates among females declined from 35.2 in 1930 to 3.0 in 2004[5,6] Nonetheless, gastric cancer remains a highly fatal condition, because the majority of patients are diagnosed with late-stage disease that is difficult to treat.[7,8]

Previous studies have demonstrated that AI/AN populations are at higher risk for this disease than the general US population.[9,10] In the Southwestern US and in Alaska, incidence rates for gastric cancer among AI/AN populations remain high despite declining rates in other racial/ethnic populations from the same regions.[9,10] However, it is likely that misclassification of AI/ANs as other races in central cancer registries[11-14] resulted in an underestimate of the true burden of gastric cancer in these populations.

This report provides a comprehensive overview of the burden of gastric cancer among AI/AN populations in the US from both nationwide and regional perspectives. Rates for NHW populations are presented for comparison. To minimize the effects of the misclassification of race for AI/ANs, cancer registry data were linked with Indian Health Service (IHS) patient services records, and the analyses were restricted to residents of counties where such linkages were most efficacious.

MATERIALS AND METHODS

Cancer Cases

Incident gastric cancer cases diagnosed during 1999 through 2004 were identified from population-based registries that participate in the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program[15] and/or the Centers for Disease Control and Prevention National Program of Cancer Registries (NPCR).[16] During the period covered by this study, participating registries classified tumor histology, tumor behavior, and primary cancer site (ie, topography) according to the Third Edition of the *International Classification of Diseases for Oncology* (ICD-O).[17]

Eligible cases included all malignant neoplasms of the stomach (ICD-O topography codes C16.0-C16.9 and ICD-O behavior code 3). Lymphomas (ICD-O histology codes 9590-9769), mesothelioma (ICD-O histology codes 9050-9055), and Kaposi sarcoma (ICD-O histology code 9140) were excluded from the analysis. Benign and in situ tumors (ICD-O behavior codes 0 and 2, respectively) also were excluded along with tumors of uncertain or unknown behavior (ICD-O behavior code 1).

Cancer registries usually document AI/AN ancestry from statements in medical and vital records. However, previous studies have demonstrated that registries often misclassify AI/ANs as other races.[11-14] For the current analysis, cancer registry records were linked with IHS patient services files to address this problem, because AI/AN individuals must provide proof of membership in a federally recognized tribe to receive healthcare from the IHS.[18]

IHS provision of healthcare to AI/AN populations is considered to be greatest in Contract Health Service Delivery Area (CHSDA) counties, which generally are defined as those counties that contain or are adjacent to federally recognized tribal reservations and/or trust lands. There is evidence that AI/AN race misclassification occurs less often in CHSDA counties.[19] For this reason, 1 set of incidence rates was calculated for residents of all US counties, and a second set of rates was calculated for residents of CHSDA counties. Figure 1 illustrates the incidence rates calculated for each of 6 IHS regions (Alaska, Pacific Coast, Northern Plains, Southern Plains, Southwest, and East) and for all regions combined. These IHS regions were chosen because they are consistent with previous reports of regional patterns of specific health outcomes and disease risk factors for AI/ANs.[20-22] Approximately 56% of the US AI/AN population resides in CHSDA counties. This proportion varies by IHS region: Alaska, 100%; East, 13.1%; Northern Plains, 59%; Southern Plains, 64.1%; Pacific Coast, 55.6%; Southwest, 87.5%. Additional details regarding CHSDA and IHS and the data sources and methods used for this analysis are provided elsewhere.[18]

Standards for coding stage of disease at diagnosis changed during the period of this study (1999-2004). To avoid incomparability among the staging schemes,[23] the analysis of stage of disease at diagno-

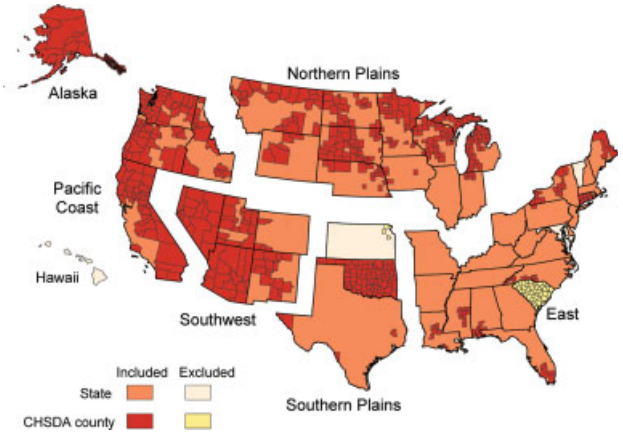

FIGURE 1. States and Contract Health Service Delivery Area counties by Indian Health Service Region.

sis was restricted to incident cases diagnosed during the years 2001 through 2003 and coded according to *SEER Summary Stage 2000*.[24] The staging categories were as follows: *localized* for disease that was restricted to the stomach, *regional* for disease that extended directly into organs and areas adjacent to the stomach, and *distant* for disease that had metastasized to portions of the body not directly adjacent to the stomach. The *undetermined* category was for those whose disease stage at diagnosis could not be determined.

The site of primary tumor within the stomach may be related to the underlying etiology of disease.[25] In general, cancers that arise in central/distal regions of the stomach are associated more closely with *H. pylori* infection than cancers in the proximal stomach. To characterize the topographic distribution of gastric cancers among AI/ANs and NHWs, cases were grouped as follows: *proximal* (cardia and fundus), *distal* (gastric body, lesser curvature, greater curvature, antrum, and pylorus), and *overlapping/unknown* (overlapping sites or unknown primary site). Because most studies of gastric cancer etiology were focused on adenocarcinoma, our analysis of cases by anatomic subsite was restricted solely to patients with adenocarcinoma.

Statistical Analyses

Average annual age-adjusted incidence rates were calculated by using the direct method.[26] Rates were expressed per 100,000 population and age-adjusted to the 2000 US standard population.[27] Age-specific rates were calculated for 4 categories: aged <40 years, ages 40 to 49 years, ages 50 to 64 years, and aged ≥ 65 years. Ratios comparing incidence rates among AI/ANs with those among NHWs were calculated by dividing the former by the latter, confidence intervals (CIs) for age-adjusted rates and standardized rate ratios (RR) were calculated based on methods described by Tiwari et al[28] using SEER*Stat version 6.3.6.[29] Denominators for rate calculations were derived from population estimates from the US Bureau of the Census.[18] Differences between AI/ANs and NHWs by categories of disease stage were evaluated with the chi-square statistic using standard modules in SAS software.[30]

RESULTS

In total, 701 incident gastric cancer cases were diagnosed among AI/ANs in participating cancer registries during the period 1999 through 2004 (Table 1). A majority of these cases (ie, 606 cases representing 86.5% of all incident cases) were diagnosed among AI/AN residents of CHSDA counties. Gastric cancer incidence rates for AI/AN populations residing in CHSDA counties were uniformly higher than rates based on AI/AN residents of all counties combined (except in Alaska, where all counties are designated as CHSDAs). In contrast, there was little difference in NHW rates between CHSDA counties and all counties combined. These findings were consistent with improved classification of AI/AN cancer cases within CHSDA counties, which increased rates for AI/ANs but had minimal effect on rates for NHWs. Consequently, all remaining findings were based on rates that were calculated for residents of CHSDA counties.

Among residents of CHSDA counties, gastric cancer incidence rates varied by geographic region, race, and sex (Table 1) (Fig. 2). Rates for AI/AN males exceeded those for NHW males in all areas except the East. Rates among AI/AN males ranged from 7.9 in the East to 34.6 in Alaska. In contrast, there was relatively little regional variation in the rates for NHW males (range, 7.1-10.1). Rates for AI/AN females exceeded those for NHW females in all IHS regions. Similar to males, there was large geographic variation in incidence among AI/AN females (range, 4.7-17.7) but not among NHW females (range, 3.0-4.4). Incidence rates were higher for males than females among both AI/ANs and NHWs in all IHS regions.

Gastric cancer incidence rates increased with age (Table 2). For all IHS regions combined, AI/AN rates exceeded NHW rates at every age. In the Northern Plains and the Southwest, incidence rates for AI/ANs were greater than rates for NHWs at every age, and the differences in Alaska were particularly

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

		CHSDA Counties						All Counties					
IHS Region	Sex	AI/AN Count	AI/AN Rate[b]	95% CI for AI/AN Rate	NHW Rate[b]	RR (AI/AN:NHW)	95% CI for RR	AI/AN Count	AI/AN Rate[b]	95% CI for AI/AN Rate	NHW Rate[b]	RR (AI/AN:NHW)	95% CI for RR
Northern Plains	Both sexes	97	13.2	10.5-16.3	5.6	2.35[c]	1.86-2.91	116	9.4	7.6-11.4	5.9	1.59[c]	1.29-1.94
	Males	58	18.7	13.6-24.9	8.5	2.21[c]	1.60-2.95	71	13.5	10.1-17.6	8.8	1.54[c]	1.15-2.01
	Females	39	9.2	6.4-12.7	3.4	2.69[c]	1.86-3.74	45	6.4	4.5-8.6	3.7	1.72[c]	1.22-2.33
Alaska[d]	Both sexes	88	24.5	19.3-30.4	5.3	4.61[c]	3.34-6.38	88	24.5	19.3-30.4	5.3	4.61[c]	3.34-6.38
	Males	52	34.6	24.8-46.6	7.7	4.46[c]	2.89-6.84	52	34.6	24.8-46.6	7.7	4.46[c]	2.89-6.84
	Females	36	17.7	12.2-24.7	3.0	5.90[c]	3.41-10.38	36	17.7	12.2-24.7	3.0	5.90[c]	3.41-10.38
Southern Plains	Both sexes	117	9.0	7.4-10.8	5.1	1.77[c]	1.44-2.15	128	7.2	5.9-8.5	5.2	1.39[c]	1.15-1.66
	Males	63	10.5	8.0-13.5	7.2	1.46[c]	1.10-1.91	68	8.1	6.2-10.3	7.6	1.06	0.81-1.37
	Females	54	7.6	5.7-9.9	3.4	2.23[c]	1.64-2.97	60	6.3	4.8-8.1	3.3	1.91[c]	1.45-2.47
Pacific Coast	Both sexes	90	7.9	6.2-9.8	5.6	1.40[c]	1.11-1.75	108	5.2	4.2-6.3	6.0	0.87	0.70-1.06
	Males	61	12.2	9.0-16.1	8.3	1.48[c]	1.09-1.95	72	7.9	5.9-10.1	8.8	0.90	0.68-1.15
	Females	29	4.7	3.1-6.7	3.5	1.34	0.88-1.94	36	3.2	2.2-4.4	3.8	0.84	0.58-1.17
East	Both sexes	20	6.1	3.6-9.5	6.9	0.88	0.52-1.38	61	2.5	1.9-3.3	6.4	0.39[c]	0.29-0.51
	Males	11	7.9	3.6-14.7	10.1	0.79	0.36-1.46	38	3.7	2.5-5.3	9.4	0.40[c]	0.27-0.56
	Females	9	4.8	2.2-9.2	4.4	1.09	0.48-2.07	23	1.7	1.0-2.5	4.2	0.40[c]	0.25-0.60
Southwest	Both sexes	194	11.5	9.9-13.3	4.9	2.37[c]	2.02-2.76	200	10.6	9.1-12.3	4.8	2.19[c]	1.88-2.54
	Males	114	15.3	12.5-18.5	7.1	2.17[c]	1.75-2.64	118	14.0	11.5-17.0	7.0	2.00[c]	1.62-2.42
	Females	80	8.6	6.8-10.8	3.0	2.86[c]	2.22-3.62	82	7.9	6.2-9.9	3.0	2.60[c]	2.03-3.27
Total	Both sexes	606	10.8	10.0-11.8	5.8	1.88[c]	1.72-2.05	701	7.2	6.7-7.8	6.1	1.19[c]	1.10-1.29
	Males	359	14.7	13.1-16.4	8.5	1.74[c]	1.55-1.95	419	9.9	8.8-10.9	8.9	1.11	0.99-1.23
	Females	247	7.9	6.9-9.0	3.6	2.18[c]	1.90-2.49	282	5.2	4.6-5.9	3.9	1.34[c]	1.18-1.51

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

CHSDA indicates Contract Health Services Delivery Area; IHS, Indian Health Service; AI/AN, American Indians/Alaska Natives; 95% CI, 95% confidence interval; NHW, non-Hispanic whites; RR, rate ratio.

[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 US standard population.

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

[d] Rates and RRs 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: 1999-2004 (41 states and the District of Columbia): Alaska,* Ala,* Ark, Ariz,* Calif,* Colo,* Conn,* DC, Del, Fla,* Ga, Hawaii, Iowa,* Idaho,* Ill, Ind,* Ky, La,* Mass,* Me,* Mich,* Minn,* Mo, Mont,* NC,* Neb,* NH, NJ, NM,* Nev,* NY,* Ohio, Okla,* Ore,* Pa,* RI,* Tex,* Utah,* Wash,* Wis,* WVa, and Wyo*; 1999 and 2002-2004: ND*; 2001-2004: SD*; 2003-2004: Miss* and Va; 2004: Tenn (asterisks indicate states with at least 1 county designated as a CHSDA).

Percent regional coverage of AI/AN in CHSDA counties versus AI/AN in all counties: Alaska, 100%; East, 13.1%; Northern Plains, 59%; Southern Plains, 64.1%; Pacific Coast, 55.6%; Southwest, 87.5%.

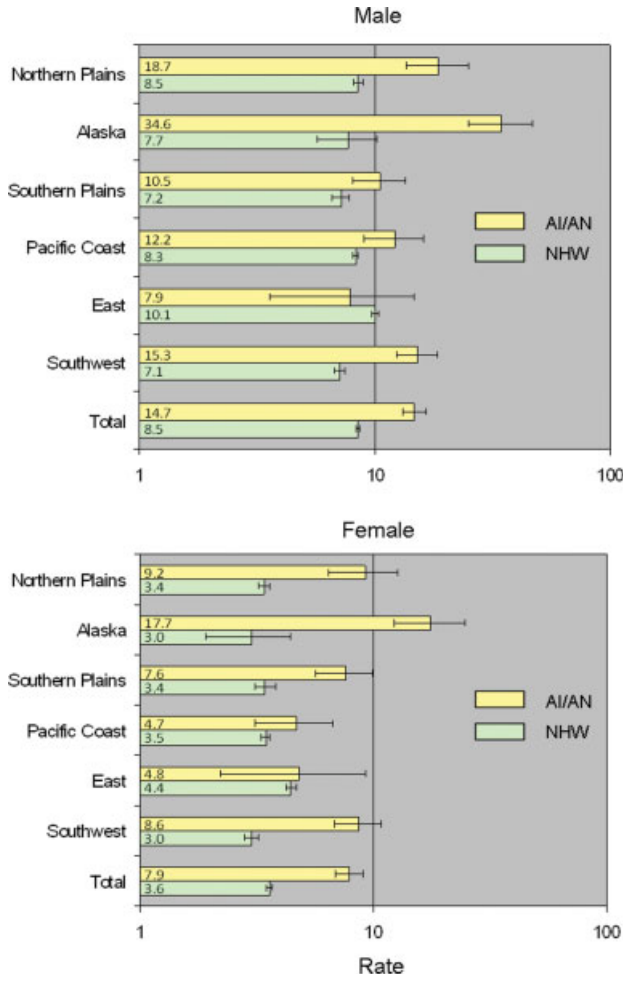

FIGURE 2. Gastric cancer incidence rates (per 100,000 population and age-adjusted to the 2000 US standard population) and corresponding 95% confidence limits for American Indians/Alaska Natives (AI/AN) and non-Hispanic whites (NHW) by sex and Indian Health Service Region and Contract Health Services Delivery Area counties, US, 1999-2004 (source: cancer registries in the Centers for Disease Control and Prevention National Program of Cancer Registries and/or the National Cancer Institute Surveillance, Epidemiology, and End Results Program).

pronounced. In the remaining IHS regions, differences between AI/ANs and NHWs were less pronounced, but AI/AN rates tended to be higher. Males rates exceeded females rates at all ages among both AI/ANs and NHWs (data not shown).

A majority of gastric cancer cases in both AI/ANs and NHWs were diagnosed at regional or distant stages of disease (data not shown). For all IHS regions combined, AI/ANs were slightly less likely than NHWs to be diagnosed at early stages of disease, but these differences did not achieve statistical significance ($P = .48$). Similar patterns were observed by geographic region.

For all IHS regions combined, incidence rates of adenocarcinoma of the proximal stomach generally were similar for AI/ANs and NHWs, whereas rates of adenocarcinoma of the central/distal stomach were higher for AI/ANs than for NHWs (Table 3). However, this pattern was not uniform across IHS regions or by sex.

DISCUSSION

Results from this study document dramatic regional variation in the incidence of gastric cancer among AI/ANs that was not observed among NHWs residing in the same geographic areas. AI/ANs in some regions were diagnosed with a higher proportion of central/distal gastric cancers, which may indicate a disproportionate burden of disease because of *H. pylori*. It is unlikely that these results were influenced substantially by the misclassification of race for AI/ANs, because this issue was addressed by linking cancer registry data with IHS databases and by restricting the analysis to residents of CHSDA counties.

The molecular biology of gastric cancer is complex and varies by gastric site and histology. The incidence of gastric cancer in the stomach cardia, which accounts for 39% of gastric cancers in US males,[31] has been increasing and may involve the same elusive risk factors that are driving increasing rates of esophageal adenocarcinoma. By comparison, rates for gastric cancer that affect other stomach sites have fallen sharply over the last half century in the US and elsewhere.[5]

Adenocarcinoma of the stomach commonly is grouped into 2 primary variants: diffuse and intestinal (well differentiated).[32] The incidence of the diffuse type of cancer is similar in most populations, suggesting that the intestinal type may be responsible for regional variation. The diffuse type of gastric cancer is more commonly hereditary, affects younger patients, and often is associated with blood group A. Hereditary diffuse gastric cancer follows an autosomal-dominant pattern and involves mutation in the cell adhesion protein E-cadherin.[33] Sporadic, nonhereditary cases involve bialleic inactivation of the cadherin 1 gene *CDH1*, which encodes for E-caderin.[34] By comparison, the intestinal type of gastric cancer is more common in older individuals, involves the stomach body and antrum, and mirrors adenocarcinoma elsewhere in the gastrointestinal tract.[35] The molecular sequence of events leading to the intestinal-type variant is not completely understood, but appears to follow a chronic gastritis-atrophy-metaplasia-dysplasia-carcinoma sequence.[36]

TABLE 2
Gastric Cancer Incidence Rates and Rate Ratios by Age and Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites in Contract Health Service Delivery Area Counties: US, 1999-2004

	<40 Years				40-49 Years				50-64 Years				≥65 Years			
IHS Region	AI/AN Rate[a]	NHW Rate[a]	RR	95% CI	AI/AN Rate[a]	NHW Rate[a]	RR	95% CI	AI/AN Rate[a]	NHW Rate[a]	RR	95% CI	AI/AN Rate[a]	NHW Rate[a]	RR	95% CI
Northern Plains	1.2	0.2	5.69[b]	2.46-11.39	7.1	2.3	3.07[b]	1.60-5.39	17.5	8.4	2.09[b]	1.35-3.09	69.6	30.8	2.26[b]	1.65-3.04
Alaska	2.2	0.1	16.27[b]	3.24-154.70	15.0	2.6	5.73[b]	2.47-13.15	26.1	6.0	4.37[b]	2.26-8.26	134.5	31.1	4.33[b]	2.83-6.61
Southern Plains	0.2	0.2	0.88	0.10-3.33	5.9	2.2	2.64[b]	1.39-4.72	13.4	7.0	1.90[b]	1.27-2.77	47.0	28.0	1.68[b]	1.29-2.16
Pacific Coast	0.2	0.2	1.05	0.21-3.03	1.8	2.3	0.79	0.29-1.74	10.9	8.5	1.29	0.86-1.86	46.0	30.4	1.51[b]	1.12-2.00
East	0.3	0.3	1.08	0.03-6.33	3.9	2.8	1.40	0.29-4.16	9.5	9.8	0.97	0.35-2.12	30.6	38.1	0.80	0.38-1.50
Southwest	0.6	0.2	3.43[b]	1.56-6.80	3.8	2.1	1.81	0.98-3.12	17.4	7.3	2.39[b]	1.78-3.14	63.2	26.5	2.39[b]	1.94-2.91
Total	0.6	0.2	2.69[b]	1.82-3.83	4.9	2.4	2.05[b]	1.57-2.64	15.1	8.4	1.78[b]	1.52-2.08	59.1	31.7	1.87[b]	1.67-2.08

Source: Cancer registries in the Center for Disease Control's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

IHS indicates Indian Health Service; AI/AN, American Indians/Alaska Natives; NHW, non-Hispanic whites; RR, rate ratio; 95% CI, 95% confidence interval.

[a] Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population.

[b] The RR is statistically significant ($P < .05$).

Years of data and registries used: 1999-2004 (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 2002-2004: North Dakota*; 2001-2004: South Dakota*; 2003-2004: Mississippi* and Virginia; 2004: Tennessee (asterisks indicate states with at least 1 county designated as a Contract Health Service Delivery Area).

Over the past 2 decades, data have been accumulating that support an increasingly strong causal relation between infection with *H. pylori* and the diagnosis of noncardia gastric adenocarcinoma.[37-39] Prospective studies in high-risk populations have reported *H. pylori* infection as a definite risk factor for development of gastric cancer.[40,41] Infection with *H. pylori* results in a chronic, active immune response that, in the absence of antibiotic-induced eradication, persists for the life of the host.

H. pylori is a common infection that causes chronic gastritis and peptic ulcer disease.[42,43] It has been characterized by the International Agency for Research on Cancer as a Class 1 carcinogen.[44] Prevalence of *H. pylori* infection is related chiefly to age and geographic location. Estimates from the current National Health and Nutrition Examination Survey revealed an overall antibody prevalence of 27.1%, with prevalence estimates approximately 20% greater for non-Hispanic black, Mexican-American, and other Hispanic groups.[45] Seroprevalence increases with age, and previous studies in the US have documented that seroprevalence among individuals aged ≥60 years is approximately 50%.[46-53] Although most data on *H. pylori* prevalence in AI/AN communities are based on work in Alaska,[54-57] where prevalence is approximately 75%, a population-based survey in an American Indian community in Montana also revealed a high prevalence (53%).[58] In developing countries, prevalence approaches 90%, with most individuals infected before age 10 years.[59,60]

Environmental factors other than *H. pylori* also influence the risk of developing gastric cancer. Consumption of fresh fruits and vegetables has been associated consistently with lowered risk of the disease.[61] Micronutrients, including vitamin E (α-tocopherol), carotenoids, selenium, and especially vitamin C (ascorbic acid), all have been linked with reduced risk, although short-term intervention trials with these nutrients has not demonstrated protective effects.[62,63] High consumption of salt, nitrite, and nitrates has been associated consistently with gastric cancer risk. Refrigeration may have played a role in reducing gastric cancer rates over the last 60 years by decreasing reliance on food-preservation methods such as salt curing, pickling, and meat smoking (the latter 2 are sources of carcinogenic N-nitroso compounds).[64,65] Cigarette smoking also has been associated with an increased risk of gastric cancer; however, the absence of control for confounders such as *H. pylori* infection and fresh produce consumption have hindered the interpretation of many studies.[66-68]

Obesity may be an important risk factor for gastric cancer of the cardia.[69] Behavioral Risk Factor Surveillance System data indicate that AI/AN populations from all regions have a higher prevalence of obesity than NHW populations.[70] Despite this finding, proximal gastric cancer incidence was only significantly higher in AI/ANs than in NHWs among males in Alaska. Family history also confers an elevated risk of gastric cancer. Between 10% and 30% of

TABLE 3
Gastric Adenocarcinoma Incidence Rates and Rate Ratios by Anatomic Subsite, Sex, and Indian Health Service Region for American Indians/Alaska Natives and Non-Hispanic Whites in Contract Health Service Delivery Area Counties: US, 1999-2004

		Males						Females					
		AI/AN		NHW		AI/AN:NHW		AI/AN		NHW		AI/AN:NHW	
IHS Region	Subsite	Rate[a]	95% CI	Rate[a]	95% CI	RR	95% CI	Rate[a]	95% CI	Rate[a]	95% CI	RR	95% CI
Northern Plains	Proximal[b]	4.7	2.3-8.2	3.8	3.6-4.1	1.23	0.60-2.16	1.9	0.7-3.9	0.8	0.7-0.9	2.45	0.91-5.10
	Central/distal[c]	6.2	3.3-10.4	1.8	1.7-2.0	3.39[e]	1.77-5.72	4.5	2.7-7.0	1.1	1.0-1.2	4.04[e]	2.37-6.41
	Other[d]	5.0	2.7-8.3	1.5	1.4-1.7	3.23[e]	1.73-5.44	2.5	1.1-4.6	0.8	0.7-0.9	3.15[e]	1.42-5.94
Alaska	Proximal[b]	14.5	8.4-22.8	3.0	2.0-4.4	4.77[e]	2.43-8.92	2.1	0.7-4.9	0.7	0.3-1.5	2.86	0.69-11.11
	Central/distal[c]	11.8	6.6-19.1	2.0	1.0-3.5	5.79[e]	2.58-13.53	11.3	6.9-17.1	0.8	0.3-1.6	14.86[e]	5.95-44.94
	Other[d]	6.5	2.4-13.1	1.2	0.5-2.2	5.55[e]	1.64-16.71	2.5	0.9-5.7	1.0	0.4-1.9	2.57	0.70-8.89
Southern Plains	Proximal[b]	4.0	2.6-6.0	2.6	2.3-3.0	1.53	0.96-2.32	1.2	0.5-2.2	0.7	0.5-0.8	1.75	0.72-3.56
	Central/distal[c]	2.5	1.4-4.1	1.7	1.4-2.0	1.44	0.77-2.46	2.8	1.7-4.3	0.9	0.8-1.1	3.02[e]	1.76-4.87
	Other[d]	2.5	1.3-4.2	1.5	1.2-1.8	1.67	0.84-2.97	2.0	1.1-3.3	0.9	0.8-1.1	2.18[e]	1.14-3.79
Pacific Coast	Proximal[b]	2.3	1.1-4.3	3.9	3.7-4.1	0.60	0.28-1.11	0.6	0.2-1.5	0.8	0.8-0.9	0.72	0.18-1.81
	Central/distal[c]	5.0	3.0-7.7	1.9	1.8-2.0	2.62[e]	1.55-4.07	1.4	0.6-2.6	1.2	1.1-1.3	1.17	0.53-2.18
	Other[d]	3.0	1.6-5.1	1.3	1.1-1.4	2.42[e]	1.27-4.11	1.8	0.8-3.3	0.7	0.7-0.8	2.50[e]	1.13-4.64
East	Proximal[b]	1.8	0.2-6.0	4.1	3.8-4.3	0.44	0.05-1.47	1.2	0.1-3.9	1.0	0.9-1.1	1.21	0.15-4.16
	Central/distal[c]	1.4	0.3-4.4	2.7	2.5-2.9	0.51	0.10-1.64	2.8	0.9-6.5	1.6	1.5-1.8	1.72	0.53-4.01
	Other[d]	2.6	0.4-7.5	1.8	1.6-1.9	1.49	0.25-4.29	0.4	0.0-2.5	0.8	0.8-0.9	0.48	0.01-2.94
Southwest	Proximal[b]	2.2	1.2-3.5	3.0	2.8-3.3	0.71	0.40-1.15	1.1	0.6-2.0	0.6	0.5-0.7	1.96	0.96-3.54
	Central/distal[c]	7.5	5.5-9.9	1.4	1.3-1.6	5.27[e]	3.80-7.13	3.4	2.3-4.9	1.0	0.8-1.1	3.51[e]	2.27-5.15
	Other[d]	2.5	1.5-3.9	1.4	1.3-1.6	1.80[e]	1.07-2.81	2.0	1.2-3.1	0.8	0.7-0.9	2.59[e]	1.49-4.16
Total	Proximal[b]	3.7	2.9-4.6	3.7	3.6-3.8	1.00	0.79-1.24	1.2	0.8-1.6	0.8	0.8-0.9	1.47[e]	1.02-2.04
	Central/distal[c]	5.5	4.5-6.6	2.0	1.9-2.1	2.75[e]	2.26-3.32	3.4	2.8-4.1	1.2	1.2-1.3	2.76[e]	2.24-3.37
	Other[d]	3.2	2.5-4.0	1.5	1.4-1.5	2.16[e]	1.67-2.75	1.9	1.5-2.5	0.8	0.7-0.8	2.46[e]	1.84-3.21

Source: Cancer registries in the Center for Disease Control's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

IHS indicates Indian Health Service; AI/AN, American Indians/Alaska Natives; NHW, non-Hispanic whites; 95% CI, 95% confidence interval; RR, rate ratio.

[a] Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population.

[b] Includes primary sites C16.0-C16.1 (topography codes from the International Classification of Diseases for Oncology).

[c] Includes primary sites C16.2-C16.6.

[d] Includes primary sites C16.8-C16.9.

[e] The RR is statistically significant ($P < .05$).

Years of data and registries used: 1999-2004 (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 2002-2004: North Dakota*; 2001-2004: South Dakota*; 2003-2004: Mississippi* and Virginia; 2004: Tennessee (asterisks indicate states with at least 1 county designated as a Contract Health Service Delivery Area).

patients with gastric cancer have a family history of the disease,[71-73] and twin studies have suggested that inherited genes contribute approximately 28% of the added risk, with environmental factors making up the remainder.[74]

In summary, this report on gastric cancer in AI/AN populations builds on previous publications by addressing the misclassification of race and by presenting incidence rates both nationwide and by region. Results from this study suggest a need to better characterize the burden of *H. pylori* among AI/ANs and NHWs and to clarify whether this factor alone is responsible for the disproportionate burden of gastric cancer in AI/AN populations. Regional differences in gastric cancer incidence in AI/AN populations may provide an opportunity to elucidate risk factors and identify future means of prevention.

REFERENCES

1. Parkin D, Whelan S, Ferlay J, Teppo L, Thomas D. Cancer Incidence in Five Continents, Vol VIII. IARC Scientific Publication No. 155. Lyon, France: International Agency for Research on Cancer; 2002.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74-108.
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across 5 continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24:2137-2150.
4. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev.* 1986;8:1-27.

5. Wingo PA, Cardinez CJ, Landis SH, et al. Long-term trends in cancer mortality in the United States, 1930-1998. *Cancer.* 2003;97(12 suppl):3133-3275.
6. 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; 110:2119-2152.
7. Dickson JL, Cunningham D. Systemic treatment of gastric cancer. *Eur J Gastroenterol Hepatol.* 2004;16:255-263.
8. Moehler M, Galle PR, Gockel I, Junginger T, Schmidberger H. Multimodal treatment of gastric cancer. *Best Pract Res Clin Gastroenterol.* 2007;21:965-981.
9. Wiggins CL, Becker TM, Key CR, Samet JM. Stomach cancer among New Mexico's American Indians, Hispanic whites, and non-Hispanic whites. *Cancer Res.* 1989;49: 1595-1599.
10. Alberts SR, Kelly JJ, Lanier AP, Sacco F. Occurrence of esophageal and gastric cancer in Alaska Natives, 1969-2003. *Alaska Med.* 2006;48:2-11.
11. Frost F, Taylor V, Fries E. Racial misclassification of Native Americans in a Surveillance, Epidemiology, and End Results cancer registry. *J Natl Cancer Inst.* 1992;84:957-962.
12. Sugarman JR, Holliday M, Ross A, Castorina J, Hui Y. Improving American Indian cancer data in the Washington State Cancer Registry using linkages with the Indian Health Service and Tribal Records. *Cancer.* 1996;78(7 suppl):1564-1568.
13. Kwong S, Perkings C, Snipes K, Wright W. Improving American Indian cancer data in the California Cancer Registry by linkage with the Indian Health Service. *J Registry Manage.* 1998;25:17-20.
14. Becker TM, Bettles J, Lapidus J, et al. Improving cancer incidence estimates for American Indians and Alaska Natives in the Pacific Northwest. *Am J Public Health.* 2002; 92:1469-1471.
15. Hankey BF, Ries LA, Edwards BK. The Surveillance, Epidemiology, and End Results Program: a national resource. *Cancer Epidemiol Biomarkers Prev.* 1999;8:1117-1121.
16. Thoburn KK, German RR, Lewis M, Nichols PJ, Ahmed F, Jackson-Thompson J. Case completeness and data accuracy in the Centers for Disease Control and Prevention's National Program of Cancer Registries. *Cancer.* 2007;109: 1607-1616.
17. Fritz A, Percy C, Jack A. International classification of diseases for oncology. Geneva, Switzerland: World Health Organization; 2000.
18. Espey DK, Wiggins CL, Jim MA, Miller BA, Johnson CJ, Becker TM. Methods for improving cancer surveillance data in American Indian and Alaska Native populations. *Cancer.* 2008;113(5 suppl):1120-1130.
19. Jim MA, Espey DK, Wiggins C, Cobb N, Wingo PA. Racial Misclassification of American Indians Residing Near IHS Facilities: Poster P-47. Presented at the 2006 North American Association of Central Cancer Registries Annual Conference, Regina, Saskatchewan, Canada, June 10-16, 2006.
20. Cobb N, Paisano RE. Patterns of cancer mortality among Native Americans. *Cancer.* 1998;83:2377-2383.
21. Denny CH, Holtzman D, Cobb N. Surveillance for health behaviors of American Indians and Alaska Natives. Findings from the Behavioral Risk Factor Surveillance System, 1997-2000. *MMWR Surveill Summ.* 2003;52:1-13.
22. Espey D, Paisano R, Cobb N. Regional patterns and trends in cancer mortality among American Indians and Alaska Natives, 1990-2001. *Cancer.* 2005;103:1045-1053.
23. Howe HL, Jamison M, Havener L, Chen VW, Ries L. Site-Specific Comparison of Summary Stage 1977 and Summary Stage 2000 Coding. Springfield, Ill: North American Association of Central Cancer Registries; 2005.
24. Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA, eds. SEER Summary Staging Manual-2000: Codes and Coding Instructions. NIH Publication No. 01-4969. Bethesda, Md: National Cancer Institute; 2001.
25. Peek P, Blaser M. *Helicobacter pylori* and gastrointestinal tract adenocarcinoma. *Nat Cancer Rev.* 2002;2:28-37.
26. Rothman K, Greenland S. Modern Epidemiology, 2nd ed. Philadelphia, Pa: Lippincott, Williams and Wilkins; 1998.
27. Klein R, Schoenborn C. Age Adjustment Using the 2000 Projected U.S. Population. Healthy People 2010 Statistical Notes. Hyattsville, Md: National Center for Health Statistics; 2001.
28. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. *Stat Methods Med Res.* 2006;15: 547-569.
29. Surveillance Research Program. SEER*Stat Software. Bethesda, Md: National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2007. Available at: http://www.seer.cancer.gov/seerstat. Accessed on April 4, 2008.
30. SAS Institute Inc. Statistical Analysis System (SAS) Software, Version 9. Cary, NC: SAS Institute Inc.; 2003.
31. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer Incidence in 5 Continents, Vol VII. IARC Scientific Publication No. 143. Lyon, France: International Agency for Research on Cancer; 1997.
32. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histolo-clinical classification. *Acta Pathol Microbiol Scand.* 1965;64:31-49.
33. Brooks-Wilson AR, Kaurah P, Suriano G, et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. *J Med Genet.* 2004;41:508-517.
34. Pedrazzani C, Corso G, Marrelli D, Roviello F. E-cadherin and hereditary diffuse gastric cancer. *Surgery.* 2007;142: 645-657.
35. Fuchs CS, Mayer RJ. Gastric carcinoma. *N Engl J Med.* 1995;333:32-41.
36. Correa P. Is gastric carcinoma an infectious disease? *N Engl J Med.* 1991;325:1170-1171.
37. Nomura A, Hankin J, Kolonel L, Wilkens L, Goodman M, Stemmermann G. Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States). *Cancer Causes Control.* 2003;14:547-558.
38. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med.* 1991;325:1127-1131.
39. Forman D, Newell DG, Fullerton F, et al. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ.* 1991;302:1302-1305.
40. You WC, Zhang L, Gail MH, et al. Gastric dysplasia and gastric cancer: *Helicobacter pylori*, serum vitamin C, and other risk factors. *J Natl Cancer Inst.* 2000;92:1607-1612.
41. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med.* 2001;345:784-789.
42. Tytgat GN, Rauws EA. Campylobacter pylori and its role in peptic ulcer disease. *Gastroenterol Clin North Am.* 1990;19: 183-196.

43. Rauws EA, Tytgat GN. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet.* 1990;335: 1233-1235.
44. International Agency for Research on Cancer. Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61. Schistosomes, Liver Flukes and *Helicobacter pylori*. Lyon, France: International Agency for Research on Cancer; 1994.
45. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and *Helicobacter pylori* infection in the United States. *Am J Epidemiol.* 2006;163:127-134.
46. Graham DY, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. *Gastroenterology.* 1991;100:1495-1501.
47. Perez-Perez G, Rothenbacher D, Brenner H. Epidemiology of *Helicobacter pylori* infection. *Helicobacter.* 2004;9(suppl 1):1-6.
48. Malaty HM, El-Kasabany A, Graham DY, et al. Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. *Lancet.* 2002;359:931-935.
49. Kruszon-Moran D, McQuillan GM. Seroprevalence of six infectious diseases among adults in the United States by race/ethnicity: data from the Third National Health and Nutrition Examination Survey, 1988-1994. *Adv Data.* 2005; 352:1-9.
50. Everhart JE. Recent developments in the epidemiology of *Helicobacter pylori*. *Gastroenterol Clin North Am.* 2000;29: 559-578.
51. Hopkins RJ, Russell RG, O'Donnoghue JM, Wasserman SS, Lefkowitz A, Morris JG Jr. Seroprevalence of *Helicobacter pylori* in Seventh-Day Adventists and other groups in Maryland. Lack of association with diet. *Arch Intern Med.* 1990;150:2347-2348.
52. Dehesa M, Dooley CP, Cohen H, Fitzgibbons PL, Perez-Perez GI, Blaser MJ. High prevalence of *Helicobacter pylori* infection and histologic gastritis in asymptomatic Hispanics. *J Clin Microbiol.* 1991;29:1128-1131.
53. Blaser M. Principles and Practice of Infectious Diseases, Vol 2, 5th ed. New York, NY: Churchill Livingston; 2000.
54. Parkinson AJ, Gold BD, Bulkow L, et al. High prevalence of *Helicobacter pylori* in the Alaska Native population and association with low serum ferritin levels in young adults. *Clin Diagn Lab Immunol.* 2000;7:885-888.
55. Bruce MG, Bruden DL, McMahon BJ, et al. Alaska sentinel surveillance for antimicrobial resistance in *Helicobacter pylori* isolates from Alaska Native persons, 1999-2003. *Helicobacter.* 2006;11:581-588.
56. Gessner BD, Baggett HC, Muth PT, et al. A controlled, household-randomized, open-label trial of the effect that treatment of *Helicobacter pylori* infection has on iron deficiency in children in rural Alaska. *J Infect Dis.* 2006;193: 537-546.
57. McMahon BJ, Bruce MG, Hennessy TW, et al. Reinfection after successful eradication of *Helicobacter pylori*: a 2-year prospective study in Alaska Natives. *Aliment Pharmacol Ther.* 2006;23:1215-1223.
58. Melius E, Sobel J, Gold B, Henderson A, Cheek J. Risk factors for *Helicobacter pylori* in a rural community—Montana: Poster 29. Presented at the 54th Annual Epidemic Intelligence Service Conference, Atlanta, Georgia, April 11-15, 2005.
59. Bardhan PK. Epidemiological features of *Helicobacter pylori* infection in developing countries. *Clin Infect Dis.* 1997;25: 973-978.
60. Taylor D, Blaser M. The epidemiology of *Helicobacter pylori* infection. *Epidemiologic Rev.* 1991;13:42-59.
61. Kelly JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol.* 2003;56:1-9.
62. La Vecchia C, Ferraroni M, D'Avanzo B, Decarli A, Franceschi S. Selected micronutrient intake and the risk of gastric cancer. *Cancer Epidemiol Biomarkers Prev.* 1994;3:393-398.
63. Hansson LE, Nyren O, Bergstrom R, et al. Nutrients and gastric cancer risk. A population-based case-control study in Sweden. *Int J Cancer.* 1994;57:638-644.
64. Kono S, Hirohata T. Nutrition and stomach cancer. *Cancer Causes Control.* 1996;7:41-55.
65. Buiatti E, Palli D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy: II. Association with nutrients. *Int J Cancer.* 1990;45:896-901.
66. Hansson LE, Baron J, Nyren O, Bergstrom R, Wolk A, Adami HO. Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer.* 1994;57:26-31.
67. Ji BT, Chow WH, Yang G, et al. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer.* 1996;77:2449-2457.
68. Gonzalez CA, Pera G, Agudo A, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer.* 2003;107: 629-634.
69. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric noncardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control.* 2005;16:285-294.
70. 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): 1131-1142.
71. Zanghieri G, Di Gregorio C, Sacchetti C, et al. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. *Cancer.* 1990;66:2047-2051.
72. Palli D, Galli M, Caporaso NE, et al. Family history and risk of stomach cancer in Italy. *Cancer Epidemiol Biomarkers Prev.* 1994;3:15-18.
73. Bernini M, Barbi S, Roviello F, et al. Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. *Gastric Cancer.* 2006;9:9-13.
74. Lichtenstein P, Holm N, Verkasalo P, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* 2000;343:78-85.