Research Article

Cancer Prevention Research

Racial/Ethnic Patterns of Young-Onset Noncardia Gastric Cancer

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Abstract

Increasing noncardia gastric cancer incidence rates among individuals age younger than 50 years have gained much attention, particularly as causes remain unknown. Using population-based NIH/NCI's Surveillance, Epidemiology, and End Results (SEER) program data from 2007 to 2015, multivariable logistic regression was used to quantify associations between race/ethnicity and clinicodemographic features among young-onset noncardia gastric cancer patients. A total of 2,872 individuals ages 20 to 49 years were diagnosed with primary noncardia gastric cancer. Age at diagnosis, insurance status, anatomic subsite, American Joint Committee on Cancer (AJCC) clinical stage, histologic type, tumor grade, surgery, and county-level smoking prevalence differed by race/ethnicity (all $P \leq 0.003$). Compared with non-Hispanic whites, Hispanics were more likely to be diagnosed at younger ages [odds ratio (OR) = 0.97; 95% confidence intervals (CI), 0.95–0.99], on Medicaid/uninsured (OR = 3.83; 95% CI, 2.89–5.08), diagnosed with higher grade tumors (OR = 1.93; 95% CI, 1.32–2.84), and less likely to undergo surgery (OR = 0.62; 95% CI, 0.44–0.88) or to reside in counties with higher smoking prevalence (OR = 0.15; 95% CI, 0.11–0.21) after adjustment for sex, subsite, and histologic type. Asian/Pacific Islanders were more likely to be female (OR = 1.40; 95% CI, 1.04–1.88), and less likely to be diagnosed with metastatic disease (OR = 0.59; 95% CI, 0.37–0.95) or to reside in counties with higher smoking prevalence (OR = 0.13; 95% CI, 0.08–0.19). Approximately two in every five patients with young-onset noncardia gastric cancer are Hispanic. Further investigation into the molecular heterogeneity of young-onset noncardia gastric cancers by race/ethnicity to understand etiologies underlying this rising disease epidemic is warranted. This population-based cohort study sheds light that biological and environmental factors may partly underlie race/ethnicity-related differences in young-onset noncardia gastric cancer susceptibility and outcomes.

Introduction

As demographics, diet, excess body weight, smoking prevalence, and exposures to other cancer-related risk factors have changed over time, the burden of noncardia gastric cancer has also evolved (1–6). Population-based studies and studies from academic institutions have both reported racial/ethnic disparities in gastric cancer incidence and outcomes among all patients or among young-onset cases (ages younger than 50 years at diagnosis) relative to older-onset cases (2, 6–8). Anderson and colleagues examined incidence rates of noncardia gastric cancer by age groups, noting that rates are rising from older to younger generations (2). Indeed, noncardia gastric cancer incidence rates have increased among young non-Hispanic white, non-Hispanic black, and Hispanic women, as well as among young men (6). Gupta and colleagues recently demonstrated that among all-comers, incident noncardia gastric cancer rate ratios were higher among non-Hispanic blacks, Hispanics, Asian or Pacific Islanders, and American Indian or Alaska Natives compared with non-Hispanic whites (9). However, no studies to date have examined racial/ethnic differences specifically within the population of young individuals diagnosed with gastric cancer. Given the increasing burden of young-onset noncardia gastric cancers (1, 2, 5, 6, 10), we evaluated racial/ethnic patterns among men and women diagnosed between the ages of 20 and 49 years with a first primary noncardia gastric cancer in the United States.

Patients and Methods

Young-onset noncardia gastric cancer cases were identified using the NIH and NCI's Surveillance, Epidemiology, and End Results (SEER) program (11). The SEER program collects data on cancer incidence and mortality from 18

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population-based cancer registries that cover approximately 28% of the U.S. population (12). The data set used is publicly available (https://seer.cancer.gov/data/access.html) and was exempt from Institutional Review Board review. This study was performed in accordance with the Declaration of Helsinki.

A case listing session in SEER*Stat was run on the SEER18 incidence data set (11) to obtain clinicodemographic features on pathologically confirmed first primary noncardia gastric cancer cases among individuals ages 20 to 49 years at diagnosis (young-onset noncardia gastric cancer cases). We restricted our analysis to young-onset noncardia gastric cancer cases diagnosed between 2007 and 2015 with known age and race/ethnicity, as 2007 is the first year for which individual-level insurance status data were available in SEER. Our final cohort was comprised of 2,872 patients diagnosed with a first primary young-onset noncardia gastric cancer.

Clinicodemographic characteristics examined included patient age at diagnosis, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/Spanish/Latino, Asian or Pacific Islander, American Indian/Alaska Native), individual-level insurance status (privately insured, Medicaid/uninsured), anatomic subsite (C16.1–C16.6), histologic type [recorded from pathology reports according to International Classification of Disease for Oncology (ICD-O) codes], tumor grade (well to moderately differentiated, poorly differentiated to undifferentiated), American Joint Committee on Cancer (AJCC) clinical tumor stage, cancer sequence (only 1 primary tumor, first of 2+ primaries), and surgical therapy as part of the first course of therapy (yes, no). Histologic types were classified into diffuse type, intestinal type, or other type, using the Lauren classification (13) previously described in Henson and colleagues (14). Based upon the Lauren classification (13), diffuse type gastric carcinoma included diffuse carcinoma (8,145); signet ring cell carcinoma (8490); and linitis plastica, a gross descriptive term referring to a signet ring cell and/or diffuse carcinoma within the stomach wall (8142). Intestinal type gastric carcinoma included: carcinoma, not otherwise specified (8010); adenocarcinoma, not otherwise specified (8140); adenocarcinoma, intestinal type (8144); and tubular adenocarcinoma (8211). All other histologic types were classified as other tumor types.

It has been previously suggested that race/ethnicity might be a proxy for socioeconomic status (15–17). For this reason, we used individual-level insurance status as an approximation of socioeconomic status. Evidence also supports that cigarette smoking is associated with increased risk of gastric cancer (18–21). Consequently, we used an area-based measure of adult smoking prevalence that is available in SEER for an approximation of current smokers. This measure was the percentage of current smokers age 18+ years taken from the Behavioral Risk Factor Surveillance System and the National Health Interview Survey to model small area estimates for current smoking prevalence between 2008 and 2010 (https://sae.cancer.gov/nhis-brfss/). On the basis of the distribution in our cohort of patients with young-onset noncardia gastric cancer, tertiles of the percentage of current adult smokers (smoking index) were created. Tertile 1 (T1) represents the third of the cohort that resides in areas where the lowest proportion of adults are current smokers, and tertile 3 (T3) represents the proportion of the cohort that resides in areas with the highest proportion of current adult smokers, divided as follows: T1: <13% current smokers age 18+ years; T2: 13 to 17% current smokers age 18+ years; and T3: 18%+ current smokers age 18+ years.

To assess patterns of young-onset noncardia gastric cancer among individuals age 20 to 49 years at diagnosis, we compared clinicodemographic features by race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/Spanish/Latino, Asian or Pacific Islander, and American Indian/Alaska Native) using χ^2 tests and t tests for categorical and continuous variables, respectively. Multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) to quantify associations between clinicodemographic features and race/ethnicity as the outcome, where the reference outcome category was non-Hispanic white individuals diagnosed with young-onset noncardia gastric cancer. Associations between clinicodemographic features and race/ethnicity were assessed in adjusted models that included: age at diagnosis, sex, individual-level insurance status, anatomic subsite, AJCC clinical stage, histologic type, tumor grade, smoking index, and the use of surgical resection, based upon patients having complete covariate information. Among patients with unknown AJCC clinical stage, reasons could include lack of information available in the patient chart, ineligibility for pathological staging, or classification criteria not met for assigning a valid AJCC stage value. Data were analyzed using SAS version 9.4 statistical software (SAS Institute). All tests were two-sided, and $P < 0.05$ was considered to be statistically significant.

Results

Between 2007 and 2015, a total of 2,872 individuals ages 20 to 49 years were diagnosed with a first primary young-onset noncardia gastric cancer. Baseline clinical and demographic characteristics of individuals by race/ethnicity are described in Table 1. Young-onset noncardia gastric cancers were most commonly diagnosed among Hispanics, as nearly 2 in every 5 individuals (37.8%) with young-onset noncardia gastric cancer were Hispanic. Non-Hispanic whites comprised approximately one-quarter (27.2%) of the population. The mean age of diagnosis was 41.6 years (SD 6.4 years) and differed by race/ethnicity, as Hispanics were more likely to be

Table 1. Summary of clinicodemographic characteristics by race/ethnicity among patients with young-onset noncardia gastric cancer: SEER18, 2007–2015

Characteristic	Total No. (%)	Non-Hispanic white No. (%)	Non-Hispanic black No. (%)	Hispanic No. (%)	Asian or Pacific Islander No. (%)	American Indian/ Alaska Native No. (%)	P^a
Total	2,872	781 (27.2)	486 (16.9)	1,086 (37.8)	478 (16.6)	41 (1.4)	
Age at diagnosis, years							0.003
20–29	175 (6.1)	43 (5.5)	24 (4.9)	83 (7.6)	24 (5.0)	1 (2.4)	
30–39	710 (24.7)	170 (21.8)	105 (21.6)	303 (27.9)	121 (25.3)	11 (26.8)	
40–49	1987 (69.2)	568 (72.7)	357 (73.5)	700 (64.5)	333 (69.7)	29 (70.7)	
Mean (SD), Years	41.6 (6.4)	42.0 (6.3)	42.4 (6.3)	40.8 (6.6)	41.7 (6.2)	42.1 (5.7)	<0.0001
Sex							0.12
Female	1,434 (49.9)	401 (51.3)	231 (47.5)	521 (48.0)	260 (54.4)	21 (51.2)	
Male	1,438 (50.1)	380 (48.7)	255 (52.5)	565 (52.0)	218 (45.6)	20 (48.8)	
Insurance status							<0.0001
Privately insured	1,796 (62.5)	603 (77.2)	282 (58.0)	539 (49.6)	360 (75.3)	12 (29.3)	
Medicaid/uninsured	983 (34.2)	142 (18.2)	182 (37.4)	524 (48.3)	108 (22.6)	27 (65.9)	
Unknown	93 (3.2)	36 (4.6)	22 (4.5)	23 (2.1)	10 (2.1)	2 (4.9)	
Anatomic Subsite							0.0026
Fundus	296 (10.3)	108 (13.8)	57 (11.7)	93 (8.6)	34 (7.1)	4 (9.8)	
Corpus	722 (25.1)	203 (26.0)	114 (23.5)	294 (27.1)	104 (21.8)	7 (17.1)	
Antrum	979 (34.1)	239 (30.6)	167 (34.4)	379 (34.9)	183 (38.3)	11 (26.8)	
Pylorus	124 (4.3)	30 (3.8)	25 (5.1)	44 (4.1)	20 (4.2)	5 (12.2)	
Lesser curvature	441 (15.4)	110 (14.1)	72 (14.8)	165 (15.2)	85 (17.8)	9 (22.0)	
Greater curvature	310 (10.8)	91 (11.7)	51 (10.5)	111 (10.2)	52 (10.9)	5 (12.2)	
AJCC clinical stage							<0.0001
0–I	510 (17.8)	175 (22.4)	78 (16.0)	146 (13.4)	104 (21.8)	7 (17.1)	
II	371 (12.9)	79 (10.1)	74 (15.2)	130 (12.0)	81 (16.9)	7 (17.1)	
III	453 (15.8)	101 (12.9)	76 (15.6)	185 (17.0)	85 (17.8)	6 (14.6)	
IV	1,128 (39.3)	263 (33.7)	177 (36.4)	509 (46.9)	161 (33.7)	18 (43.9)	
Unknown	410 (14.3)	163 (20.9)	81 (16.7)	116 (10.7)	47 (9.8)	3 (7.3)	
Histologic type							<0.0001
Diffuse	1,192 (41.5)	248 (31.8)	169 (34.8)	542 (49.9)	217 (45.4)	16 (39.0)	
Intestinal	892 (31.1)	203 (26.0)	176 (36.2)	320 (29.5)	173 (36.2)	20 (48.8)	
Other	788 (27.4)	330 (42.3)	141 (29.0)	224 (20.6)	88 (18.4)	5 (12.2)	
Tumor grade							<0.0001
I/II (well to moderately differentiated)	476 (16.6)	176 (22.5)	88 (18.1)	138 (12.7)	66 (13.8)	8 (19.5)	
III/IV (poorly differentiated to undifferentiated)	1,754 (61.1)	377 (48.3)	269 (55.3)	743 (68.4)	340 (71.1)	25 (61.0)	
Unknown	642 (22.4)	228 (29.2)	129 (26.5)	205 (18.9)	72 (15.1)	8 (19.5)	
Cancer sequence							0.14
Only one primary	2,772 (96.5)	745 (95.4)	466 (95.9)	1,059 (97.5)	462 (96.7)	40 (97.6)	
First of 2+ primaries	100 (3.5)	36 (4.6)	20 (4.1)	27 (2.5)	16 (3.3)	1 (2.4)	
Surgery							<0.0001
None	1,188 (41.4)	275 (35.2)	197 (40.5)	543 (50.0)	156 (32.6)	17 (41.5)	
Yes	1,642 (57.2)	494 (63.3)	281 (57.8)	529 (48.7)	314 (65.7)	24 (58.5)	
Unknown	42 (1.5)	12 (1.5)	8 (1.6)	14 (1.3)	8 (1.7)	0 (0.0)	
Smoking index[b]							<0.0001
<13% current smokers	1,123 (39.1)	194 (24.8)	83 (17.1)	587 (54.1)	257 (53.8)	2 (4.9)	
13%–17% current smokers	675 (23.5)	201 (25.7)	104 (21.4)	213 (19.6)	153 (32.0)	4 (9.8)	
18%+ current smokers	975 (33.9)	386 (49.4)	299 (61.5)	187 (17.2)	68 (14.2)	35 (85.4)	

NOTE. *P* value calculations do not include unknown values.

[a]Pairwise *P* values are presented in Fig. 1.

[b]Tertiles of the percentage of current smokers age 18+ years on the basis of the distribution in our cohort of patients with young-onset noncardia gastric cancer.

diagnosed at younger ages (40.8 years) compared with non-Hispanic whites, non-Hispanic blacks, Asian or Pacific Islanders, or American Indian/Alaska Natives (42.0, 42.4, 41.7, and 42.1 years, respectively; $P < 0.0001$). Individual-level insurance status, anatomic subsite, AJCC clinical stage, histologic type, tumor grade, surgical resection, and county-level adult smoking prevalence also statistically significantly differed by race/ethnicity (all $P \leq 0.003$; Table 1 and Fig. 1).

Over half (59.2%) of young-onset noncardia gastric cancers were located in the corpus and antrum (Table 1). Differences by disease stage were most pronounced between non-Hispanic whites or Asian/Pacific Islanders and Hispanic individuals—while approximately one-third (33.7%) of young-onset noncardia gastric cancers were diagnosed at stage IV among non-Hispanic whites as well as Asian or Pacific Islanders, nearly half (46.9%) of cases among Hispanics presented with metastatic disease (pairwise $P < 0.0001$; Table 1 and Fig. 1). By histologic type, 41.5% of young-onset noncardia gastric cancers were of the diffuse type (which includes diffuse carcinomas, signet ring cell carcinomas, and

Characteristic		NHW	NHB	Hispanic	API	AI/AN
Age at diagnosis	NHW		0.90	0.0007	0.34	0.56
	NHB			0.002	0.39	0.61
	Hispanic				0.06	0.43
	API					0.75
	AI/AN					
Sex	NHW		0.19	0.15	0.29	0.99
	NHB			0.87	0.03	0.65
	Hispanic				0.019	0.68
	API					0.70
	AI/AN					
Individual insurance status	NHW		<0.0001	<0.0001	0.09	<0.0001
	NHB			0.0003	<0.0001	0.0003
	Hispanic				<0.0001	0.01
	API					<0.0001
	AI/AN					
Anatomic subsite	NHW		0.45	0.008	0.0005	0.08
	NHB			0.29	0.13	0.30
	Hispanic				0.21	0.09
	API					0.18
	AI/AN					
AJCC clinical stage	NHW		0.003	<0.0001	0.01	0.51
	NHB			0.007	0.21	0.96
	Hispanic				<0.0001	0.72
	API					0.64
	AI/AN					
Histologic type	NHW		<0.0001	<0.0001	<0.0001	0.0002
	NHB			<0.0001	0.0001	0.06
	Hispanic				0.03	0.03
	API					0.25
	AI/AN					
Tumor grade	NHW		0.02	<0.0001	<0.0001	0.36
	NHB			0.0002	0.004	0.96
	Hispanic				0.79	0.19
	API					0.24
	AI/AN					
Cancer sequence	NHW		0.68	0.01	0.27	0.51
	NHB			0.08	0.53	0.60
	Hispanic				0.34	0.98
	API					0.75
	AI/AN					
Surgery	NHW		0.05	<0.0001	0.36	0.46
	NHB			0.0006	0.01	0.98
	Hispanic				<0.0001	0.25
	API					0.28
	AI/AN					
Smoking index	NHW		<0.0001	<0.0001	<0.0001	<0.0001
	NHB			<0.0001	<0.0001	0.009
	Hispanic				0.22	<0.0001
	API					<0.0001
	AI/AN					

Figure 1.
Summary of pairwise *P* values between race/ethnicities by clinicodemographic characteristics among patients with young-onset noncardia gastric cancer. *P* values are presented for all pairwise comparisons. Associations with $P < 0.05$, $P < 0.01$, and $P < 0.001$ are highlighted in light, medium, and dark gray colors, respectively. NHW, non-Hispanic white; NHB, non-Hispanic black; API, Asian or Pacific Islander; AI/AN, American Indian/Alaska Native; AJCC, American Joint Committee on Cancer.

linitis plastica; Table 1). Non-Hispanic whites were least likely to present with poorly differentiated to undifferentiated (grade III/IV) tumors across racial/ethnic groups. Over half of young individuals (57.2%) diagnosed with noncardia gastric cancer underwent surgery as part of the first course of therapy. Among young-onset noncardia gastric cancer patients, American Indian/Alaska Natives and non-Hispanic blacks were most likely to reside in areas with the highest prevalence of current adult smokers.

To evaluate associations between race/ethnicity and clinicodemographic features among individuals diagnosed with young-onset noncardia gastric cancer, we performed adjusted multivariable logistic regression

Table 2. Multivariable logistic regression for clinicodemographic factors by race/ethnicity among patients with young-onset noncardia gastric cancer: SEER18, 2007–2015

	Adjusted model[b]							
	Non-Hispanic black[a]		Hispanic[a]		Asian or Pacific Islander[a]		American Indian/Alaska Native[a]	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age at diagnosis								
Years (continuous)	1.01 (0.99–1.04)	0.32	0.97 (0.95–0.99)	0.008	0.99 (0.97–1.02)	0.60	1.02 (0.96–1.10)	0.50
Sex								
Male	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
Female	1.15 (0.85–1.55)	0.37	1.02 (0.79–1.32)	0.86	1.40 (1.04–1.88)	0.025	1.17 (0.53–2.60)	0.70
Insurance status								
Privately insured	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
Medicaid/uninsured	1.94 (1.39–2.69)	<0.0001	3.83 (2.89–5.08)	<0.0001	1.25 (0.88–1.78)	0.21	6.27 (2.75–14.26)	<0.0001
Anatomic subsite								
Fundus	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
Corpus	1.41 (0.78–2.54)	0.26	1.11 (0.68–1.80)	0.69	1.00 (0.55–1.82)	1.00	1.01 (0.17–5.97)	0.99
Antrum	1.57 (0.89–2.78)	0.12	1.00 (0.62–1.61)	1.00	1.21 (0.68–2.16)	0.52	1.20 (0.23–6.21)	0.83
Pylorus	1.62 (0.67–3.88)	0.28	1.26 (0.60–2.67)	0.54	1.27 (0.53–3.05)	0.59	7.57 (1.20–47.81)	0.03
Lesser curvature	1.38 (0.74–2.58)	0.31	1.07 (0.63–1.82)	0.80	1.31 (0.70–2.45)	0.40	1.58 (0.29–8.63)	0.60
Greater curvature	1.04 (0.49–2.18)	0.93	1.17 (0.65–2.11)	0.60	1.12 (0.55–2.26)	0.76	3.20 (0.53–19.44)	0.21
AJCC clinical stage								
0–I	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
II	1.82 (1.12–2.96)	0.016	1.36 (0.88–2.10)	0.17	1.26 (0.79–2.01)	0.34	1.39 (0.36–5.33)	0.63
III	1.18 (0.73–1.93)	0.50	1.26 (0.83–1.91)	0.28	0.86 (0.54–1.36)	0.51	0.80 (0.21–3.10)	0.75
IV	0.89 (0.54–1.44)	0.62	0.81 (0.53–1.22)	0.31	0.59 (0.37–0.95)	0.031	1.10 (0.30–3.96)	0.89
Histologic type								
Diffuse	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
Intestinal	1.35 (0.95–1.90)	0.09	0.95 (0.71–1.28)	0.74	1.28 (0.92–1.79)	0.15	1.27 (0.53–3.05)	0.60
Other	0.72 (0.44–1.20)	0.20	0.68 (0.45–1.04)	0.08	0.55 (0.33–0.91)	0.02	0.33 (0.06–1.84)	0.20
Tumor grade								
I/II	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
III/IV	1.23 (0.81–1.87)	0.34	1.93 (1.32–2.84)	0.001	1.91 (1.22–2.97)	0.005	0.95 (0.31–2.87)	0.92
Surgery								
None	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
Yes	0.75 (0.50–1.14)	0.17	0.62 (0.44–0.88)	0.007	1.10 (0.72–1.67)	0.66	0.86 (0.29–2.52)	0.78
Smoking index[c]								
<13% current smokers	Ref (—)		Ref (—)		Ref (—)		Ref (—)	
13%–17% current smokers	1.13 (0.73–1.76)	0.58	0.54 (0.40–0.74)	0.0001	0.54 (0.38–0.76)	0.0004	2.12 (0.38–11.90)	0.39
18%+ current smokers	1.79 (1.22–2.62)	0.003	0.15 (0.11–0.21)	<0.0001	0.13 (0.08–0.19)	<0.0001	5.69 (1.29–25.02)	0.021

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; OR, odds ratio.

[a]Referent group is non-Hispanic white patients with young-onset primary noncardia gastric cancer.

[b]Adjusted for age at diagnosis, sex, anatomic subsite, insurance status, AJCC clinical stage, histologic type, tumor grade, surgery, and smoking index.

[c]Tertiles of the percentage of current smokers age 18+ years on the basis of the distribution in our cohort of patients with young-onset noncardia gastric cancer.

analysis (Table 2). Age at diagnosis was inversely associated with Hispanic race/ethnicity (OR 0.97; 95% CI, 0.95–0.99, $P = 0.008$). Compared with non-Hispanic whites with young-onset noncardia gastric cancer, Hispanics were also more likely to be on Medicaid/uninsured (OR 3.83; 95% CI, 2.89–5.08, $P < 0.0001$), and were nearly twice as likely to be diagnosed with higher grade (III/IV) tumors (OR 1.93; 95% CI, 1.32–2.84, $P = 0.001$). Hispanic individuals were 38% less likely to undergo surgery (OR 0.62; 95% CI, 0.44–0.88, $P = 0.007$) and were 46% to 85% less likely to reside in counties with higher prevalence of adult smoking (T2: OR 0.54; 95% CI, 0.40–0.74, $P = 0.0001$; T3: OR 0.15; 95% CI, 0.11–0.21, $P < 0.0001$). Although young non-Hispanic blacks were 82% more likely to be diagnosed with stage II noncardia gastric cancers (OR 1.82; 95% CI, 1.12–2.96, $P = 0.016$), no associations with advanced-stage (stage III/IV) disease were observed among young non-Hispanic blacks versus non-Hispanic whites.

Asian or Pacific Islanders with young-onset noncardia gastric cancer were statistically significantly more likely to be female (OR 1.40; 95% CI, 1.04–1.88, $P = 0.025$) and were 41% less likely to be diagnosed with metastatic disease (OR 0.59; 95% CI, 0.37–0.95, $P = 0.031$) compared with young non-Hispanic white individuals. Similar to Hispanics, Asian or Pacific Islanders with young-onset noncardia gastric cancer were also nearly twice as likely to be diagnosed with grade III/IV tumors (OR 1.91; 95% CI, 1.22–2.97, $P = 0.005$) and were 46% to 87% less likely to reside in counties with a higher prevalence of adult smoking (T2: OR 0.54; 95% CI, 0.38–0.76, $P = 0.0004$; T3: OR 0.13; 95% CI, 0.08–0.19, $P < 0.0001$) versus non-Hispanic whites (Table 2). Aligned with evidence that American Indians/Alaska Natives have one of the highest cigarette smoking prevalences of all racial/ethnic groups (19–21), American Indian/Alaska Native individuals with young-onset noncardia gastric cancer were over 5-fold more likely to reside in areas with the highest adult smoking prevalence compared with young

non-Hispanic whites (T3: OR 5.69; 95% CI, 1.29–25.02, $P = 0.021$; Table 2).

Discussion

Young-onset noncardia gastric cancer incidence rates are rising alarmingly, with underlying causes unknown (1–3, 5–7, 10). Our investigation of 2,872 individuals diagnosed with young-onset noncardia gastric cancer in the United States from 2007 to 2015 identified racial/ethnic disparities by tumor grade, county-level adult smoking prevalence, age at diagnosis, and sex. Approximately two in every five patients with young-onset noncardia gastric cancer were Hispanic. Further, Hispanic individuals were more likely to be diagnosed at younger ages and with high-grade tumors, and were less likely to undergo surgery or reside in counties with higher prevalence of adult smoking compared with non-Hispanic whites. Asian/Pacific Islanders diagnosed with young-onset noncardia gastric cancer were more likely to be female and to be diagnosed with high-grade tumors, and were less likely to be diagnosed with metastatic disease or to reside in counties with higher adult smoking prevalence. American Indian/Alaska Natives diagnosed with young-onset noncardia gastric cancer were more likely to reside in areas with the highest prevalence of current adult smokers. To our knowledge, this population-based cohort study is the first to evaluate clinicodemographic characteristics, including tumor grade, county-level smoking prevalence, and race/ethnicity, within the population of individuals diagnosed with young-onset noncardia gastric cancer.

The landscape of race/ethnicity is evolving across the United States, and Hispanics are expected to account for nearly one-third of the population by year 2060 (22). Aligned with these changing demographics, Islami and colleagues revealed gastric noncardia adenocarcinoma rates increased in younger age groups among men (across racial/ethnic groups) as well as among non-Hispanic white, non-Hispanic black, and Hispanic women using nationwide data from the North American Association of Central Cancer Registries (6). Balakrishnan and colleagues (10) reported that gastric cancer incidence remained stable among non-Hispanic whites and non-Hispanic blacks, but noted a significant rise in incidence among Hispanic adults in a cancer registry-based study among all patients across a single county in Texas. A recent retrospective study in Mexico examined clinicopathologic features of gastric carcinomas in Latin patients and noted an increased incidence of gastric cancer among patients age 40 years and younger compared with patients over the age of 40 years at diagnosis (5). Using the National Cancer Database, De and colleagues reported significant differences in race/ethnicity between individuals age younger than 40 years versus those 40 years of age and older diagnosed with gastric adenocarcinoma in a similar sized cohort, as Hispanic individuals were significantly more likely to be diagnosed with gastric adenocarcinoma at younger ages—concordant with our results (7). Rona and colleagues also compared clinicopathologic features and outcomes among patients diagnosed with gastric carcinoma at an academic institution and noted a higher incidence of advanced-stage tumors, poorly differentiated (grade III) carcinomas, and signet-cell type tumors among young patients—of which the majority were Hispanics—when compared with older counterparts (8). Consistent with these findings, our population-based study suggests that approximately two in every five patients diagnosed with young-onset noncardia gastric cancer in the United States are Hispanic. Further, we observed that Hispanic individuals were also more likely to be diagnosed with high-grade (grade III/IV) tumors. Hispanics with young-onset noncardia gastric cancer were more likely to be on Medicaid or uninsured, and were less likely to undergo surgery compared with non-Hispanic whites. Together with population-based findings that noncardia gastric cancer incidence rates are rising among young (age younger than 50 years) non-Hispanic white and Hispanic individuals (2, 4, 23), and that higher rates of *Helicobacter pylori* seropositivity are detected among Mexican Americans compared with non-Hispanic white adults (24), our novel findings in this population of young individuals suggest that additional research is needed to examine clinicopathologic characteristics of noncardia gastric cancers among Hispanic/Spanish/Latino subpopulations by country of origin. Genetic ancestral heritage and gene-environment interactions (25–28) may contribute to these pronounced racial/ethnic disparities in young-onset noncardia gastric cancer.

It is estimated that approximately 14% of all adults in the United States are current smokers, and that approximately 4 of every 10 cancer cases are linked to tobacco use (29). Evidence also supports that cigarette smoking is associated with an increased risk of gastric cancer (18–21), and cigarette smoking rates sharply differ by race/ethnicity. In particular, American Indian/Alaska Natives have one of the highest cigarette smoking prevalences across all racial/ethnic groups (19–21), and the risk for gastric cancer is higher among American Indian/Alaska Native young adults compared with non-Hispanic whites (30). Aligned with these patterns, we observed that American Indian/Alaska Natives with young-onset noncardia gastric cancer were more likely to reside in areas with the highest prevalence of current adult smokers versus young non-Hispanic whites. Together with other environmental exposures including diet, excess body weight, and microbiome composition (2, 23, 27, 31, 32), these health behaviors may be contributing to distinct molecular phenotypes of young-onset gastrointestinal tumors by race/ethnicity. Additional studies are needed to investigate the role of these environmental exposures and health behaviors by race/ethnicity

on young-onset gastrointestinal cancer outcomes.

Although our findings suggest racial/ethnic differences in noncardia gastric cancer within the population of young individuals, we acknowledge limitations of our study. SEER does not collect individual-level data on environmental exposures and lifestyle/behavioral factors (e.g., *Helicobacter pylori* infection, history of cigarette smoking, dietary patterns) or molecular phenotypes of tumors, does not include complete information about chemotherapy and/or radiotherapy, and there could exist potential reporting differences in clinical stage by race/ethnicity, as well as the small sample size in some racial/ethnic (e.g., American Indian/Alaska Native) groups. Given that race/ethnicity is classified based on self-identification in SEER, it is subject to misclassification. Our findings raise the possibility that interactions between noncardia gastric tumor biology and treatments might contribute to racial/ethnic differences among young patients, particularly by disease stage. However, our study does not provide complete data about treatment regimens nor the molecular phenotypes of tumors among individuals with young-onset noncardia gastric cancer.

Nevertheless, our examination of the racial/ethnic patterns of young-onset noncardia gastric cancer using a population-based cohort yields important implications for gastric cancer risk assessment and prevention. The inherent clinical heterogeneity of gastric cancer is reflected in distinct molecular subtypes of cancer cells, where integrative genomic and proteomic patterns have characterized four molecular subtypes of disease that predict survival and adjuvant chemotherapy outcomes among patients of all ages diagnosed with gastric carcinoma (33). These molecular characteristics of gastric cancer have also revealed intriguing molecular phenotypes of gastric tumors by age at diagnosis, as patients with the genomically stable subtype—associated with the poorest prognosis, the least benefit from adjuvant chemotherapy, and less distinctive genomic alterations—were diagnosed at younger ages relative to patients with the other subtypes (33). By race/ethnicity, a single institution study revealed differences in mutation rates among all-comers diagnosed with gastric adenocarcinoma, as non-Hispanic black patients were found to have higher rates of *TP53* mutations compared with non-Hispanic whites, Hispanic, or Asian/Pacific Islander cases (34). Importantly, noncardia gastric cancer has a distinct disease biology from adenocarcinoma arising in the cardia, which is much more similar to esophagogastric junction and lower esophagus (Siewert I tumors) cancers in terms of natural history and risk factors for oncogenesis (35, 36). Together, these results suggest that distinct molecular phenotypes of gastric tumors may be associated with differential response to therapies, and evaluation of these phenotypes by race/ethnicity specifically among young patients with noncardia gastric cancer could have significant implications for the clinical management of these patients.

In conclusion, these novel findings support that biological and environmental (e.g., *Helicobacter pylori* infection, cigarette smoking, diet) factors (4, 18, 21, 23, 24, 27, 31, 32, 35) may partly underlie race-related differences in young-onset noncardia gastric cancer susceptibility and outcomes. Studies are warranted to further investigate the heterogeneity of malignancies among individuals diagnosed with young-onset noncardia gastric cancer.

Disclosure of Potential Conflicts of Interest

M.A. Lewis is an advisory board member for Shire Pharmaceuticals. The authors declare no potential conflicts of interest with this work. C.M.U. has as cancer center director oversight over research funded by several pharmaceutical companies, but has not received funding directly herself.

Authors' Contributions

Conception and design: A.N. Holowatyj, M.A. Lewis
Development of methodology: A.N. Holowatyj
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.N. Holowatyj
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.N. Holowatyj, C.M. Ulrich, M.A. Lewis
Writing, review, and/or revision of the manuscript: A.N. Holowatyj, C.M. Ulrich, M.A. Lewis
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.N. Holowatyj, C.M. Ulrich, M.A. Lewis
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