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Original Article

Examining factors underlying geographic disparities in early-onset colorectal cancer survival among men in the United States

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Abstract: *Background:* Despite overall incidence reduction in colorectal cancer (CRC) the past 32 years, unexplained incidence and mortality rates have increased significantly in younger adults ages 20-49. To improve understanding of sex-specific differences among this population, we aimed to determine the variance in early-onset CRC (EOCRC) survival among US men diagnosed with CRC before age 50, while considering individual- and county-level CRC outcome determinants. *Methods:* Hotspots (i.e., counties with high EOCRC mortality rates) were derived from Centers for Disease Control and Prevention data from 1999-2017, and linked to SEER data for men aged 15-49 years with CRC. Cox proportional hazards models were used to compare CRC-specific survival probability and hazard in hotspots versus non-significant counties. A generalized R^2 was used to estimate the total variance in EOCRC survival explained by clinicodemographic and county-level determinants. *Results:* We identified 232 hotspot counties for EOCRC-214 (92%) of which were in the South. In hotspots, 1,009 men were diagnosed with EOCRC and 31,438 in non-significant counties. After adjusting for age, race, tumor stage and grade, surgery, chemotherapy, radiation therapy, and marital status, men residing in hotspot counties had higher hazard of CRC-specific death (HR 1.24, 95% CI, 1.12-1.36). Individual/county-level factors explained nearly 35% of the variation in survival, and adult smoking served as the strongest county-level determinant of EOCRC survival. *Conclusion:* Distinct geographic patterns of EOCRC were predominantly located in the southern US. Survival after EOCRC diagnosis was significantly worse among men residing in hotspot counties.

Keywords: Colorectal cancer, early-onset, racial disparities, SEER, smoking

Introduction

Colorectal cancer (CRC) affects 1 in 23 men and 1 in 25 women in their lifetime [1]. Among individuals aged ≥50, declining CRC incidence and mortality rates are attributable partly to increased CRC screening utilization and adjuvant therapy advancements [2, 3]. However, these reductions in disease burden have coincided with increased CRC incidence among individuals aged <50 (early-onset CRC [EOCRC]), such that individuals born circa 1990 have double and quadruple the risk of colon and rectal cancers, respectively, compared with similarly aged adults born around 1950 [4]. While approximately 1 in 10 new CRC diagnoses affect young individuals, the causes underlying this increase in EOCRC incidence remain unexplained [2-13]. Moreover, it is predicted that by 2030, CRC incidence rates will increase by 90%-124% among Americans aged 20-34 and by 28%-46% among those aged 35-49 [11].

EOCRC harbors a distinct clinical and molecular phenotype compared with CRC seen among

individuals aged ≥50 [14-18]. Studies have demonstrated that individuals diagnosed with EOCRC present with more advanced and aggressive stages of the disease [3, 5, 6, 19], while others have reported that younger individuals have better outcomes compared with their older counterparts [5, 6, 19]. These complex findings may be attributed to differences in environmental, geographical, and lifestyle factors (e.g., diet, obesity, sedentary behaviors), as well as sex and race/ethnicity [20].

In the US, CRC incidence and survival differ by sex, race/ethnicity, and geography. Regarding sex-specific differences, CRC incidence rates among men are nearly one-third higher than that of women, with mortality rates also 40% higher in men than in women [2]. Racial/ethnic disparities have grown more pronounced [3, 7, 8, 21], with survival after CRC diagnosis poorer among African Americans/Blacks compared with Whites, even among patients with early-stage CRC [9, 22-24]. In particular, non-Hispanic (NH) Black men have the lowest five-year CRC survival and age-adjusted mortality rates across all racial/ethnic and sex subgroups [25]. Geographically, patterns of CRC incidence and mortality have shifted over time across the US. Once highest in the Northeast, CRC mortality rates are now highest in the South and Midwest-a shift largely explained by higher birthrates and poorer economic status among Southern and Midwestern Blacks [2]. This shift holds true for EOCRC, with previous studies [26-30] identifying similar differences in geographical regions. Moreover, previous research by Siegel et al. derived contemporary spatial clusters of US counties with high CRC rates based on county-level mortality data from 1970-2011 and identified three distinct hotspots [30], yet failed to elucidate factors contributing to the troubling and sharp rise in EOCRC. Accordingly, our study aimed to identify mortality hotspots specific to men with EOCRC-a missed opportunity to improve our understanding of EOCRC disparities while controlling for sex-specific differences. Further, we examined differences in the individual- and county-level characteristics between EOCRC hotspots and non-hotspots, as well as study factors that explain better survival among men residing within EOCRC hotspots.

Material and methods

EOCRC hotspots

To identify EOCRC hotspots, we obtained county-level estimates using our previously described geospatial methodology [31]. Using data from the Centers for Disease Control and Prevention's (CDC's) underlying causes of death file [32], EOCRC deaths were defined as deaths among US residents aged 15-54 from 1999-2017. (Those aged 50-54 were included to account for patients diagnosed at age 49 with standardized 5-year follow-ups). EOCRC county-level frequencies, crude rates, and age-adjusted rates were identified using *International Classification of Diseases, Tenth Revision* (ICD-10) codes for colon- and rectum-specific cancers (Supplementary Table 1). Geospatial analyses were performed using three geospatial autocorrelation measures: empirical Bayes (EB) smoothed EOCRC mortality rates, local indicators of spatial association (LISA), and the Getis-Ord Gi* statistic [33-35]. Contiguous US counties were categorized as hotspots if they had high rates of EOCRC mortality based on all three geospatial methodologies (i.e., in the fifth quintile of smoothed EB EOCRC mortality rates (Supplementary Figure 1), a high-high cluster using LISA (Supplementary Figure 2), and an EOCRC hotspot as defined by the Getis-Ord Gi* statistic (Supplementary Figure 3)) [13, 35]. All other US counties were categorized as non-significant spots. These categories were subsequently linked to Surveillance, Epidemiology, and End Results (SEER) data [36], with patients residing in either an EOCRC hotspot or a non-significant county according to their county of residence.

Study population

Data were obtained from the National Cancer Institute (NCI) SEER program database (November 2018 submission) [36], which covers nearly one-third of the US population and includes detailed information from 18 population-based registries on demographics, clinical characteristics, and survival for each cancer diagnosis. Study participants were NH-White, NH-Black, and Hispanic adults or adolescents aged 15-49 at primary CRC diagnosis. A total of 32,447 men in the SEER database were diagnosed with EOCRC from 1999-2016, after

excluding those diagnosed with a prior malignant cancer (*n*=2,211), those with an unknown surgical procedure (*n*=243), those with missing follow-up time (*n*=28), and those residing in Alaska and Hawaii (*n*=764). Residents of Alaska and Hawaii were excluded because residence categorization in a geospatial hotspot was dependent upon counties located in the 48 contiguous states.

Statistical analysis

Differences in patient-level characteristics and county-level determinants between men residing in EOCRC hotspots and men living in non-significant counties were examined using Chi-square tests for categorical variables, analysis of variance (ANOVA) for parametric continuous variables, and Wilcoxon rank-sum tests for non-parametric continuous variables. Survival time was calculated from date of diagnosis to the last date of follow-up or the date of death. Patient follow-up was within 22 months of the annual survey submission date (November 2017). A two-sided *P*-value <0.05 was considered statistically significant. All county population proportion estimates included the total adult population.

Kaplan-Meier curves were used to compare overall hotspot residence survival among NH-Black, NH-White, and Hispanic patients. To determine the association of hotspot residence with CRC survival, multilevel regression models accounting for clustering among SEER registry groups were employed. Adjusted and unadjusted Cox proportional hazards models estimated EOCRC survival. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated. Age was included in adjusted models since the association of patient-level characteristics with residence in a hotspot was not defined *a priori*. Models were adjusted for patient-level factors found in bivariate analysis to reach statistical significance and in a separate analysis they were also adjusted for smoking at the community level which is known to be associated with cancer mortality. Other community level covariates were not considered in the multivariable modeling to avoid multicollinearity as they all were found to have significant correlation with smoking.

To estimate total EOCRC variance explained by each explanatory factor (clinicodemographic and county-level determinants) and all combined, we calculated generalized R^2 using methods adapted for Cox proportional hazards model developed by Allison [37] and based onthe Cox and Snell [38] method. Data were analyzed using SAS v9.4 (SAS Institute Inc., Cary, NC) and GeoDa v1.6.7.9 (https://geodacenter.github.io/), and mapped using ArcGIS v10.5 (Esri, Redlands, CA). Additional methods are detailed in Supplementary Methods. This study was exempt from approval by the Institutional Review Boards of the University of Utah and Augusta University because the datasets used are publicly available.

Results

Hotspot characteristics

Based on geospatial analyses using national mortality data from 1999-2017, a composite hotspot map was created for EOCRC mortality (**Figure 1**). A total of 232 (7.5%) of 3,108 contiguous US counties were EOCRC hotspots. Overall, 92% (214 of 232) of the hotspot counties were located in the South and 8% (18 of 232) were located in the Midwest (*P*<0.01; Supplementary Table 2). Hotspot counties and associated EOCRC mortality are outlined in Supplementary Table 3. Approximately 3.11% of men diagnosed with EOCRC in SEER (*n*= 1,009) resided in hotspot counties (**Figure 1**; **Table 1**). The mean EOCRC diagnosis age was 42.73 and did not significantly differ by hotspot residence (**Table 1**). Compared to men living in non-significant counties, men residing in hotspot counties were more likely to be NH-Black (30.82% vs 13.06%) and less likely to be Hispanic (1.68% vs 16.65%; *P*<0.01). Men diagnosed with EOCRC living in hotspots were significantly less likely to be married or to have a domestic partner compared to counterparts residing in non-hotspot counties (52.1% vs 56.5%, respectively; *P*<0.01). Approximately one-third of men (28.75%) had right-sided tumors. However, tumor sidedness did not significantly differ by hotspot residential status. Men residing in hotspots were more likely to be diagnosed with metastatic disease (stage IV CRC) compared to those residing in non-significant spots (2.58% vs 1.94%; *P*<0.01) (**Table 1**).

Men living in hotspot counties at EOCRC diagnosis were significantly more likely to reside in areas with greater proportions of NH-Whites

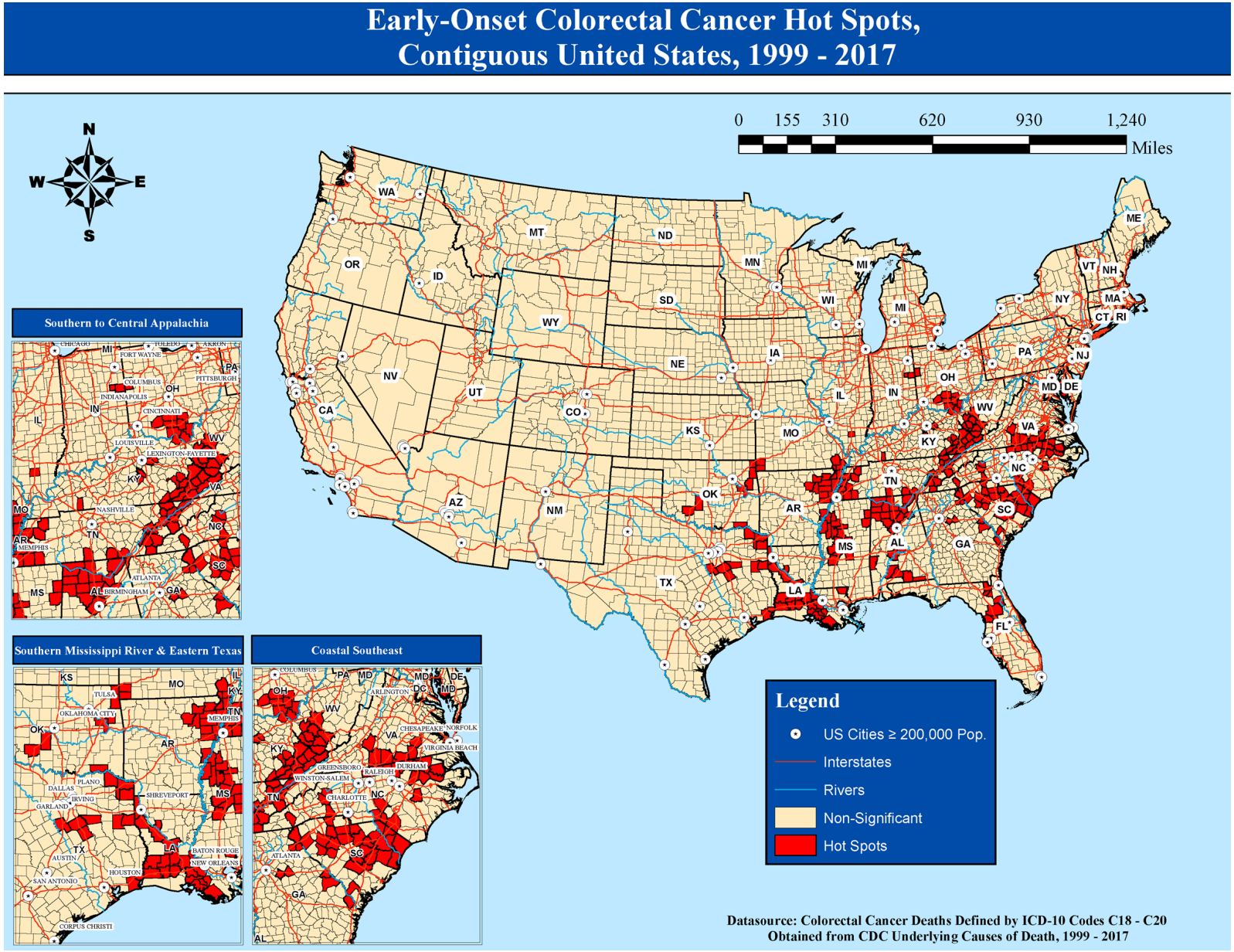

Figure 1. Early-onset colorectal cancer (CRC) mortality hotspots across the contiguous United States: US residents, 1999-2017.

Table 1. Summary of Demographic and Clinical Characteristics by EOCRC Hotspot Classification Among US Men: SEER18, 1999-2016

	Number of Cases (*N*=32,447)	EOCRC Hot-spot Residence *N* (%)		
		Hotspot[a]	Non-Significant	*P*-value[b]
	N (%) or Mean (SE)[c]	*N* (%) or Mean (SE)[c]	*N* (%) or Mean (SE)[c]	
Total	32447 (100.0)	1009 (3.11)	31438 (96.89)	<.01
Mean survival, months[d]	128.65 (0.55)	113.76 (3.01)	129.04 (0.56)	<.01
Age in years, mean	42.73 (0.04)	42.98 (0.21)	42.73 (0.04)	.23
Age at diagnosis (%)				
15-29 years	1738 (5.35)	53 (5.26)	1685 (5.36)	.17
30-39 years	6225 (19.19)	184 (18.24)	6183 (19.21)	
40-49 years	24,484 (75.46)	772 (76.51)	23,712 (75.42)	
Race (%)				
NH-White	19,657 (60.58)	663 (65.71)	18,994 (60.42)	<.01
NH-Black	4417 (13.61)	311 (30.82)	4106 (13.06)	
Hispanic	5251 (16.18)	17 (1.68)	5234 (16.65)	
Other	3122 (9.87)	18 (1.78)	3104 (9.63)	
Marital status (%)				
Single or never married	9478 (29.21)	291 (28.84)	9187 (29.22)	<.01
Married or domestic partner	18,293 (56.38)	526 (52.13)	17,767 (56.51)	
Divorced, separated, or widowed	2821 (8.69)	116 (11.50)	2705 (8.60)	
Unknown	1855 (5.72)	76 (7.53)	1779 (5.66)	
AJCC stage (%)				
0-I	5019 (15.47)	189 (18.73)	4830 (15.36)	.05
II	5968 (18.39)	170 (16.85)	5798 (18.44)	
III	8551 (26.38)	260 (25.77)	8291 (26.37)	
IV	7115 (21.93)	222 (22.00)	6893 (28.93)	
Unknown	5794 (17.86)	168 (16.65)	5626 (17.90)	
Tumor Sidedness (%)				
Right[e]	9329 (28.75)	288 (28.54)	9041 (28.76)	.88
Left[f]	23118 (71.25)	721 (71.46)	22397 (71.24)	
Grade (%)				
I (well differentiated)	3060 (9.43)	65 (6.44)	2995 (9.53)	<.01
II (moderately differentiated)	17,822 (54.93)	581 (57.58)	17,241 (54.84)	
III (poorly differentiated)	5385 (16.60)	152 (15.06)	5233 (16.65)	
IV (undifferentiated)	636 (1.96)	26 (2.58)	610 (1.94)	
Unknown	5544 (17.09)	185 (18.33)	5359 (17.05)	
Surgery (%)	27,561 (84.94)	858 (85.03)	26,703 (84.94)	.93
Chemotherapy (%)	18,574 (57.24)	18,005 (57.27)	569 (56.39)	.58
Radiation Therapy (%)	7626 (23.50)	253 (25.07)	7373 (23.45)	.23

[a]Patients residing in counties with high EOCRC mortality rates (fulfilling all three criteria for geographic clustering). [b]*p*-value calculations determined using Chi-square, t tests, log-rank test (survival), or Wilcoxon rank-sum test as appropriate. *P* value calculations do not include unknown values. [c]Presented as number (column percentage) or mean (standard error). [d]Calculated using Kaplan-Meier method (or product limit method). [e]Defined as ICD-O-3 codes 180, 181, 182, 183, and 184. [f]Defined as ICD-O-3 codes 185, 186, 187, 188, 189, 199, 209, and 260.

(66.70% vs 55.05%; *P*<0.01) and NH-Blacks (27.89% vs 11.77%; *P*<0.01; **Table 2**) compared to men living in non-significant counties. Moreover, hotspots were more likely than non-significant counties to have higher poverty rates (26.57% vs 16.77%), greater prevalence of adult obesity (34.94% vs 25.89%), more physical inactivity (32.31% vs 21.63%), fewer

Table 2. Summary of county-level characteristics by EOCRC hotspot classification among US men: SEER, 1999-2016 linked with 2014 American community survey and county health rankings county-level data

County Characteristic	EOCRC Hotspot Residence Among All Men			
	Hotspot[a] *n*=1,009 (3.11%)	Non-significant *n*=31,438 (96.89%)	*P*-value[b]	Spearman (ρ) Correlation Coefficient
	Presented as Mean (SE)[c]			
Race				
% NH-White	66.70 (0.58)	55.05 (0.12)	<0.01	0.95
% NH-Black	27.89 (0.54)	11.77 (0.07)	<0.01	0.14
% Hispanic	2.62 (0.04)	21.86 (0.10)	<0.01	-0.25
% Household income <$20,000	26.57 (0.18)	16.77 (0.03)	<0.01	0.24
% Access to exercise opportunities	52.67 (0.52)	83.36 (0.11)	<0.01	-0.24
% Limited access to healthy foods	8.58 (0.15)	4.66 (0.02)	<0.01	0.14
% Obesity	34.94 (0.09)	25.89 (0.03)	<0.01	0.26
% Smoking	23.97 (0.10)	15.44 (0.03)	<0.01	0.24
% Completed college	16.14 (0.14)	30.68 (0.06)	<0.01	-0.24
% Physical inactivity	32.31 (0.10)	21.63 (0.03)	<0.01	0.27
% Unemployed	8.11 (0.07)	9.25 (0.01)	<0.01	-0.09
% Uninsured	20.06 (0.05)	17.91 (0.03)	<0.01	0.08
PCP[d] per 100,000 persons	58.28 (0.84)	75.45 (0.15)	<0.01	-0.10
% Non-urban (rural)	43.66 (0.83)	12.70 (0.12)	<0.01	0.22
Violent crimes per 100,000 persons	488.71 (8.86)	406.75 (1.27)	<0.01	0.07

[a]County characteristic determined by patient FIPS code. Patients residing in counties with high EOCRC mortality (fulfilling all three criteria for geographic clustering). [b]Significance determined using Wilcoxon test. [c]Mean (standard error). [d]PCP = primary care physicians.

exercise opportunities (52.67% vs 83.36%), more limited access to healthy foods (8.58% vs 4.66%), lower college completion rates (16.14% vs 30.68%), higher adult smoking rates (23.97% vs 15.44%), higher uninsured rates (20.06% vs 17.91%), fewer primary care physicians (58.28 vs 75.45 per 100,000 population), increased rurality (43.66% vs 12.70%), and more violent crimes (488.7 vs 406.75 crimes per 100,000 persons) (all *P*<0.01).

Hot-spots and CRC-specific survival

Men living in hotspots had poorer CRC survival compared with those in non-significant counties (113.76 vs 129.04 months, respectively; *P*<0.001; **Table 1**). By race/ethnicity, NH-White men residing in EOCRC hotspots experienced significantly worse CRC survival compared with NH-White men in non-significant counties (*P*< 0.01; **Figure 2A**). In particular, NH-White men living in hotspots saw a 10-year survival rate of 49.31% (± SE 2.38%), while their non-significant counterparts saw 58.76% (± SE 0.42%) survival during the same time period (data not shown). However, racial disparities in survival by residential hotspot area did not persist among NH-Black or Hispanic men (*P*=0.59 and *P*=0.23, respectively; **Figure 2B** and **2C**). Among men diagnosed with EOCRC, those residing in hotspots demonstrated a 24% higher hazard for CRC-specific death compared with those residing in non-significant counties (HR 1.24, 1.12-1.36; **Table 3**). However, after adjusting for county-level smoking, men in hotspots demonstrated a 12% higher hazard for CRC-specific death (HR 1.12, 1.01-1.24). Compared with NH-White men, NH-Black (HR 1.31, 1.25-1.38) and Hispanic (HR 1.12, 1.07-1.19) patients demonstrated a 31% and 12% increased risk for CRC-specific death, respectively, after adjusting for smoking. Men who underwent surgical resection for CRC had a 61% reduced risk for CRC-specific death compared to those who did not undergo surgery (HR 0.39, 0.37-0.41). In addition, for each unit increase in the county-level proportion of adult smokers, men diagnosed with EOCRC were nearly four times more likely to die from CRC (HR 3.71, 2.52-5.45). When limited to men re-

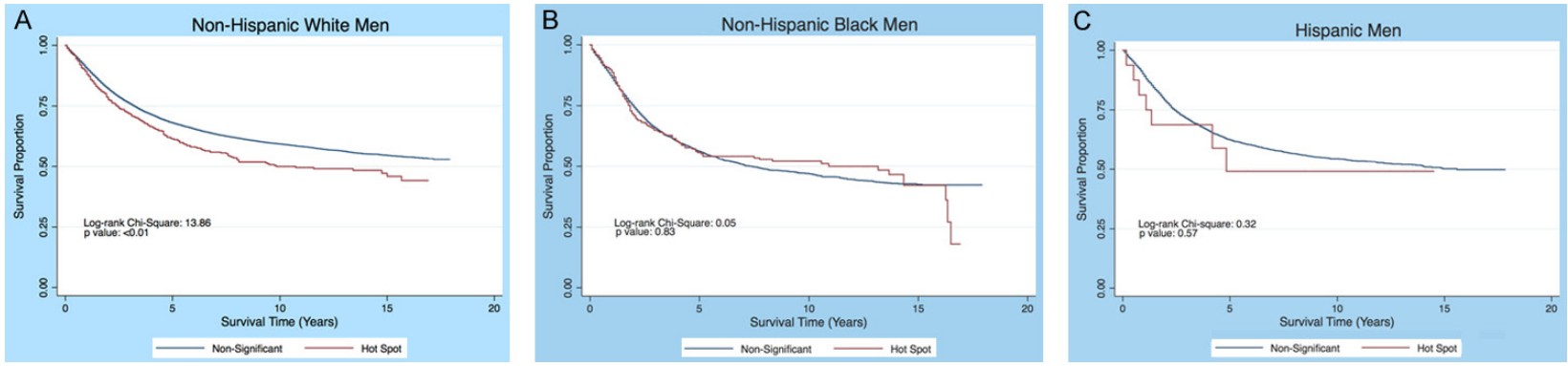

Figure 2. Kaplan-Meier CRC-specific survival curves for (A) non-Hispanic White, (B) non-Hispanic Black, and (C) Hispanic men with EOCRC by hotspot region: SEER18 1999-2015.

Table 3. Multivariable Cox Proportional Hazards Regression Models for CRC-Specific Death Among Men with EOCRC

	CRC Survival		
	No. of Deaths (%)[a]	Adjusted HR (95% CI)[b,c,d] excluding smoking	Adjusted HR (95% CI)[b,c,d] including smoking
EOCRC hotspot			
Non-significant	11,183 (34.47)	Ref	Ref
Hotspot	420 (1.29)	**1.24 (1.12-1.36)**	**1.12 (1.01-1.24)**
Age (in years)			
15-24	193 (0.59)	**0.83 (0.72-0.96)**	**0.83 (0.71-0.96)**
25-29	336 (1.04)	**0.87 (0.78-0.97)**	**0.87 (0.77-0.97)**
30-34	675 (2.08)	**0.85 (0.78-0.92)**	**0.84 (0.78-0.92)**
35-39	1442 (4.44)	0.95 (0.90-1.01)	0.95 (0.90-1.01)
40-44	2714 (8.36)	**0.91 (0.87-0.95)**	**0.91 (0.87-0.95)**
45-49	6243 (24)	Ref	Ref
Race/ethnicity			
Non-Hispanic White	6867 (21.16)	Ref	Ref
Non-Hispanic Black	1987 (6.12)	**1.32 (1.26-1.39)**	**1.31 (1.25-1.38)**
Hispanic	1814 (5.59)	**1.09 (1.03-1.14)**	**1.12 (1.07-1.19)**
Asian/Pacific Islander	827 (2.55)	0.95 (0.88-1.02)	1.00 (0.93-1.07)
Other/Unknown	108 (0.33)	**0.67 (0.55-0.81)**	**0.66 (0.55-0.80)**
Marital status			
Single or never married	3934 (12.12)	**1.38 (1.32-1.44)**	**1.39 (1.33-1.45)**
Married or domestic partner	5886 (18.14)	Ref	Ref
Divorced, separated, or widowed	1286 (3.96)	**1.37 (1.29-1.46)**	**1.36 (1.28-1.45)**
Unknown	497 (1.53)	1.02 (0.93-1.12)	1.01 (0.92-1.11)
AJCC stage			
0 or I	653 (2.01)	Ref	Ref
II	1258 (3.88)	**1.76 (1.60-1.94)**	**1.76 (1.59-1.94)**
III	2926 (9.02)	**3.34 (3.05-3.66)**	**3.34 (3.05-3.66)**
IV	5825 (17.95)	**14.06 (12.85-15.39)**	**14.12 (12.90-15.47)**
Unknown	941 (2.90)	**1.70 (1.54-1.89)**	**1.70 (1.53-1.88)**
Tumor grade			
I (well differentiated)	606 (1.87)	Ref	Ref
II (moderately differentiated)	5825 (17.95)	**1.24 (1.14-1.35)**	**1.23 (1.13-1.34)**
III (poorly differentiated)	2785 (8.58)	**1.97 (1.80-2.16)**	**1.97 (1.80-2.15)**
IV (undifferentiated)	314 (0.97)	**2.39 (2.08-2.74)**	**2.33 (2.03-2.68)**
Unknown	2073 (6.39)	**1.32 (1.20-1.45)**	**1.32 (1.20-1.45)**
Tumor surgery			
Yes	8332 (25.68)	**0.39 (0.37-0.40)**	**0.39 (0.37-0.41)**
No	3271 (10.08)	Ref	Ref
Chemotherapy			
Yes	8150 (25.12)	**0.83 (0.79-0.87)**	**0.83 (0.79-0.87)**
No or unknown	3453 (10.64)	Ref	Ref
Radiation therapy			
Yes	2949 (9.09)	**1.06 (1.01-1.11)**	**1.06 (1.02-1.11)**
No or unknown	8654 (26.67)	Ref	Ref
Smoking[e]	N/A	-	**3.71 (2.52-5.45)**
Generalized R^2			35%

[a]Number of events/deaths and row (strata) proportion. [b]Adjusted for age, race, marital status, stage, grade, surgery, chemotherapy, radiation therapy, and smoking (depending on column), while accounting for clustering by SEER registry. [c]HR = hazard ratios, estimated using multilevel Cox proportional hazards regression. [d]Bold indicates significance with *P*-value ≤ 0.05. [e]County-level proportion of adult smoking.

siding in hotspot counties, later stage (stage II-IV) CRC diagnosis was associated with increased CRC-specific mortality risk, after adjusting for county-level smoking (**Table 4**). Specifically, compared to stage 0 or I diagnosis, men diagnosed with stage II (HR 2.45, 1.60-3.75), stage III (HR 4.18, 2.76-6.32), and stage IV (HR 10.83, 7.21-16.25) had 2.5 times, 4 times, and nearly 11 times greater risk of CRC-specific mortality, respectively. Furthermore, within hotspot counties, the severity of tumor grade was associated with increased CRC-specific mortality risk, with poorly differentiated tumors (HR 1.87, 1.03-3.40) and undifferentiated tumors (HR 2.60, 1.21-5.61) having nearly 2 times and 2.6 times greater mortality risk compared to well differentiated tumors, respectively. Within hotspot counties, single men (HR 1.43, 1.13-1.79) and those who were divorced, separated, or widowed (HR 1.43, 1.05-1.95) had 43% increased risk for CRC mortality compared to married or coupled men.

Within non-significant counties, younger men aged 15-24 (HR 0.83, 0.72-0.97), 25-29 (HR 0.87, 0.77-0.97), and 30-34 (HR 0.85, 0.79-0.93) saw a 13% to 17% decrease in CRC-specific mortality risk compared to older men aged 45-49 (**Table 4**). Within non-significant counties, NH-Blacks (HR 1.33, 1.26-1.40) and Hispanics (HR 1.12, 1.07-1.19) had a 33% and 12% greater risk of CRC-specific death than NH-Whites, respectively. Furthermore, patients who had received chemotherapy had a 17% decreased risk for CRC mortality (HR 0.83, 0.79-0.87), while those who had received radiation therapy had a 7% increased risk for CRC mortality (HR 1.07, 1.02-1.12). Additionally, for each unit increase in the county-level proportion of adult smokers, men in non-significant counties were 3.5 times more likely to die from CRC-related mortality (HR 3.54, 2.39-5.23). Like the trends witnessed within hotspots, marital status and tumor stage, grade, and surgery were all associated with risk of CRC-specific mortality among men in non-significant spots.

We estimated the proportion of variance explained in CRC survival by clinicodemographic determinants and county-level smoking among men with EOCRC (**Tables 3**, **4**). Among all men, the full model determinants-including smoking-accounted for 35% of the variation in survival; the presence of smoking in the model had minimal influence on the proportion of variance explained (**Table 3**). Among all determinants, AJCC stage explained the largest proportion (15.4%) of variance in survival. Among men living in CRC hotspots, all determinants in the model accounted for nearly 32% of the survival variation (**Table 4**), with AJCC stage contributing to 13.8% of the variance. Among those living in non-significant counties, full model variables explained roughly 35% of the CRC survival variation, with AJCC stage accounting for 15.5% of the variance.

Discussion

Our analysis of CDC mortality data identified hotspot counties with high EOCRC mortality rates, mostly concentrated in the Southern US. Our analysis of outcomes for 32,447 men aged 15-49 diagnosed with CRC between 1999-2016 identified significantly worse survival for men residing in hotspot counties, who had 24% greater hazard of CRC-specific mortality compared to their non-significant counterparts. These findings are novel, given our study is one of the first to identify EOCRC mortality hotspots in the US and the first population-based study to identify county-level CRC outcome determinants specific to men diagnosed with CRC before age 50.

Among individuals of all ages diagnosed with CRC, cancer death rates vary sharply by US geographic region [39]. Previous work by Siegel et al. derived contemporary spatial clusters of US counties with high CRC rates based on county-level mortality data from 1970-2011 and identified three distinct hotspots: the lower Mississippi Delta, west-central Appalachia, and eastern Virginia/North Carolina [40]. More recently, examination of statewide variation in EOCRC incidence revealed highest incidence rates in the South [30]. Aligned with these findings, our use of three geospatial techniques defined hotspots for CRC mortality specifically among individuals diagnosed with EOCRC-which includes counties clustered in southern to central Appalachia, the southern Mississippi River and eastern Texas, and the coastal southeast and eastern Virginia/North Carolina. Moreover, we observed that men diagnosed with EOCRC residing in hotspot counties experienced a significantly higher hazard of death compared with men residing in other US

Table 4. Multivariable cox proportional hazards models for CRC-specific death among men with EO-CRC stratified by hotspot Counties

	Among Men Living in EOCRC Hotspots		Among Men Living in Non-Significant Counties	
	No. of Deaths (%)[a]	HR (95% CI)[b,c,d]	No. of Deaths (%)[a]	HR (95% CI)[b,c,d]
Age (in years)				
15-24	5 (1.19)	0.48 (0.19-1.20)	188 (1.68)	**0.83 (0.72-0.97)**
25-29	10 (2.38)	0.77 (0.40-1.48)	326 (2.92)	**0.87 (0.77-0.97)**
30-34	25 (5.95)	0.73 (0.48-1.11)	650 (5.81)	**0.85 (0.79-0.93)**
35-39	46 (10.95)	0.85 (0.62-1.18)	1396 (12.48)	0.96 (0.90-1.02)
40-44	92 (21.90)	0.88 (0.69-1.13)	2622 (23.45)	**0.91 (0.87-0.95)**
45-49	242 (57.62)	Ref	6001 (53.66)	Ref
Race/ethnicity				
NH-White	269 (64.05)	Ref	6598 (59.00)	Ref
NH-Black	139 (33.10)	1.14 (0.92-1.42)	1848 (16.53)	**1.33 (1.26-1.40)**
Hispanic	7 (1.67)	1.33 (0.62-2.84)	1807 (16.16)	**1.12 (1.07-1.19)**
Asian/PI	2 (0.48)	0.74 (0.18-3.04)	825 (7.38)	1.00 (0.93-1.07)
Other/Unknown	3 (0.71)	1.44 (0.45-4.63)	105 (0.94)	**0.65 (0.54-0.80)**
Marital status				
Single or never married	133 (31.67)	**1.43 (1.13-1.79)**	3801 (33.99)	**1.38 (1.32-1.44)**
Married or domestic partner	209 (49.76)	Ref	5677 (50.76)	Ref
Divorced, separated, or widowed	53 (12.62)	**1.43 (1.05-1.95)**	1233 (11.03)	**1.36 (1.28-1.45)**
Unknown	25 (5.95)	1.09 (0.71-1.69)	472 (4.22)	1.00 (0.91-1.10)
AJCC stage				
0 or I	38 (9.05)	Ref	615 (5.50)	Ref
II	60 (14.29)	**2.45 (1.60-3.75)**	1198 (10.71)	**1.74 (1.57-1.92)**
III	118 (28.10)	**4.18 (2.76-6.32)**	2808 (25.11)	**3.33 (3.03-3.66)**
IV	174 (41.43)	**10.83 (7.21-16.25)**	5651 (50.53)	**14.32 (13.04-15.72)**
Unknown	30 (7.14)	1.44 (0.88-2.38)	911 (8.15)	**1.72 (1.54-1.91)**
Grade				
I (well differentiated)	13 (3.10)	Ref	593 (5.30)	Ref
II (moderately differentiated)	212 (50.48)	1.14 (0.65-2.02)	5613 (50.19)	**1.23 (1.13-1.35)**
III (poorly differentiated)	87 (20.71)	**1.87 (1.03-3.40)**	2698 (24.13)	**1.97 (1.80-2.16)**
IV (undifferentiated)	15 (3.57)	**2.60 (1.21-5.61)**	299 (2.67)	**2.31 (2.01-2.66)**
Unknown	93 (22.14)	**1.89 (1.04-3.43)**	1980 (17.71)	**1.30 (1.18-1.43)**
Tumor surgery				
Yes	317 (31.42)	**0.39 (0.30-0.51)**	8015 (25.49)	**0.39 (0.37-0.41)**
No	103 (10.21)	Ref	3168 (10.08)	Ref
Chemotherapy				
Yes	276 (65.71)	0.78 (0.61-1.01)	7874 (70.41)	**0.83 (0.79-0.87)**
No or Unknown	144 (34.29)	Ref	3309 (29.59)	Ref
Radiation therapy				
Yes	112 (26.67)	1.04 (0.82-1.32)	8346 (74.63)	**1.07 (1.02-1.12)**
No or Unknown	308 (73.33)	Ref	2837 (25.37)	Ref
Smoking[e]	N/A	8.43 (0.84-84.57)	N/A	**3.54 (2.39-5.23)**
Generalized R^2		32%		35%

[a]Number of events/deaths and row (strata) proportion. [b]Adjusted for age, race, marital status, AJCC stage, grade, surgery, chemotherapy, radiation therapy, and smoking, while accounting for clustering by SEER registry. [c]HR = hazard ratios, estimated using multilevel Cox proportional hazards regression. [d]Bold indicates significance with *P*-value ≤ 0.05. [e]County-level proportion of adult smoking.

regions. Potential explanations for poorer EO-CRC outcomes among men residing in these hotspots include an enduring history of unique challenges (e.g., inadequate access to care, poor health literacy, and low educational attainment) [41-44]. We also noted that hotspot

counties had higher rates of poverty and uninsurance, as well as fewer primary care physicians. Among all determinants, AJCC clinical stage explained the largest proportion of the variance in EOCRC survival among men in hotspots and non-significant counties combined. As stage is a prognostic CRC survival determinant, these findings emphasize the importance of developing targeted prevention and treatment guidelines for EOCRC, particularly among individuals residing in regions with poorer EOCRC outcomes.

Importantly, beyond geographic disparities in survival among patients diagnosed with EOCRC, other differences persist by race/ethnicity and sex. In a previous study using the South Carolina Central Cancer Registry, Wallace et al. found that African-American patients aged <50 with advanced-stage CRC diagnosis had a significantly higher death risk than their European-American counterparts [45]. Consistent with these earlier findings [3, 7-9, 21-24], we reported higher EOCRC burden among NH-Black men in hotspots compared to non-significant counties, as well as worse survival among NH-Black men compared to NH-White men in non-significant counties. The disproportionate burden of EOCRC among NH-Black men may result from distinctive stressors coupled with cultural and social expectations that impact screening and care behaviors [46-49]. A US population-based study by Holowatyj et al. that identified racial/ethnic disparities among patients with EOCRC also reported significantly worse cancer-specific and overall survival among men compared with women [9]. Given the exacerbated burden of EOCRC among men, our study focused solely on men to identify determinants of geographic CRC survival variation while minimizing the potential impact that sex-specific differences may have on EOCRC-related outcomes. Moreover, our complimentary investigation into community health behaviors and variation in EOCRC survival among US women-explored in Holowatyj et al. [50]-reported findings in contrast to men, in which AJCC clinical stage and race/ethnicity accounted for a higher proportion of EOCRC survival variance among women in hotspot counties compared to other counties. Given these distinct variations in EOCRC survival, our results warrant further investigation into the health behaviors and molecular differences of EOCRC by race/ethnicity and sex to better understand the rising burden of this disease in young patients.

Our examination of geographic variance in EOCRC incidence and mortality among men explained by individual- and county-level characteristics is the first population-based study to shed light on modifiable determinants of EOCRC outcomes. Much of the variance accounted for in EOCRC survival in both hotspot and non-significant counties was explained by disease stage [51]. While estimated that approximately 14% of all US adults are current smokers, we observed 24% of the adult population residing in hotspot counties reported currently smoking and having smoked at least 100 cigarettes in their lifetime [52]. Moreover, we discovered that the effect of hotspots on CRC survival was reduced by 12% after adjusting for county-level smoking, suggesting that smoking may be a major contributor to the increased mortality within hotspots. Although the implementation of tobacco control programs has led to sharp declines in adult cigarette smoking over the last decade, cancers linked to tobacco use, including CRC [53-55], continue to account for approximately 4 out of every 10 cancer diagnoses and approximately 3 out of every 10 cancer deaths in the US [51, 56, 57]. As current cigarette smoking rates differ by US census region (with the highest rates among adults living in the Midwest and South), as well as by sex, race/ethnicity, education, income, and marital status [58], our findings increase awareness regarding the impact of patient characteristics on differences in EOCRC survival in hotspots versus other regions. A recent retrospective study by Wolbert et al. reported that the rate of early-onset rectal cancer in rural Appalachia was 1.5 times higher than national rates, and that smoking was strongly associated with early-onset rectal cancer [59]. Several studies have also reported that smoking is more strongly associated with rectosigmoid junction/rectal cancer than with colon cancer [60-62]. Given higher rates of smoking in men, combined with gene-tobacco interactions [63], future studies should examine how the carcinogenic effects of tobacco smoke may be uniquely contributing to EOCRC burden among men.

Current smoking is also associated with several CRC risk factors, including lower consumption of healthy foods (e.g., fruits, vegetables, fiber)

[64-67] and greater physical inactivity [68]. Along with finding a higher prevalence of adult smokers in counties with high EOCRC mortality rates, we also identified significantly higher proportions of adults having no leisure-time physical activity and more limited access to healthy foods when compared with other areas. Over time, chronic excessive caloric intake and physical inactivity lead to energy imbalances, resulting in individuals becoming overweight or developing obesity, which increases CRC risk [69, 70]. A recent study by Nguyen et al. also demonstrated that prolonged sedentary behaviors-a surrogate for a more-inactive lifestyle, are associated with increased EOCRC risk [71]. The United Health Foundation's annual report recently documented that the states in which our hotspots were located are some of the least healthy states in the country [45]. With obesity rates having nearly tripled worldwide since 1975 and with more than 70% of US adults currently overweight or obese [72], further studies of the association between lifestyle factors-including smoking, obesity, and dietary patterns-and EOCRC incidence and mortality are needed.

Our study had several limitations. First, we were unable to estimate EOCRC mortality rates in areas with limited deaths, as CDC data are suppressed at the county level when the number of deaths is fewer than 10. However, our geospatial analysis was strengthened by the use of three spatial autocorrelation methods, including the EB smoothed-rate method that accounted for counties with few cases, and the examination of mortality data across the contiguous US over the study period. Additionally, the use of FIPS codes derived from CDC death certificates and SEER patient files is a robust method of identifying EOCRC hotspots among men. However, we were unable to account for length or change of residence, which could contribute to changes in socioeconomic status, access to and quality of care, and CRC outcomes. Moreover, SEER lacks data on individual-level characteristics and lifestyle factors known to be associated with CRC risk, including individual smoking status and environmental exposures (e.g., secondhand smoke), and family CRC history and hereditary cancer syndromes. Another limitation is our aggregation of SEER data, a 17-year period from 1999 to 2016, which allowed us to work with a large, cohesive sample size, but restricted our ability to account for temporal changes relevant to CRC during this timeframe, such as advancements in cancer prevention, treatment, and epidemiology, as well as evolving clinicodemographics. In addition, we linked 1999-2016 SEER data with 2014 county-level daasets, which applied a single fixed timestamp of health and community characteristics to years of older data, which likely experienced changing characteristics over time.

Conclusions

As one of the first studies to define geographic hotspots for EOCRC, we observed significantly worse survival after EOCRC diagnosis among men-particularly NH-Black men-residing in hotspot counties. Further studies of CRC-related health behaviors among NH-Black men diagnosed with EOCRC are needed and could have significant implications for cancer screening, early detection, and care. Given that CRC incidence rates among individuals aged <50 are continuing to rise with causes unknown [3, 5, 6, 9, 19, 22-24], examination of individual-level health behaviors and clinical characteristics among men diagnosed with EOCRC is needed to explore gene-environment interactions associated with geographic survival variation and to tailor clinical algorithms for early CRC detection.

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Disclosure of conflict of interest

None.

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Supplementary Methods

Patients and methods

Study population

Clinical, demographic, and tumor characteristics and first course of treatment were obtained from SEER for men diagnosed with EOCRC over the study period [35]. Demographic characteristics included age at diagnosis, marital status, race/ethnicity, and year of diagnosis. Clinical and tumor characteristics included: American Joint Committee on Cancer (AJCC) clinical stage, tumor grade, and primary CRC sidedness (left vs right). Left-sided tumors were classified as those with International Classification of Diseases for Oncology (ICD-0-3) codes 185, 186, 187, 188, 189, 199, 209, and 260; right-sided tumors were categorized as those with ICD-0-3 codes 180, 181, 182, 183, and 184. First course of treatment was defined as receipt of surgical resection (yes/no). County-level demographic and socioeconomic data and availability of health services/community resources were obtained from two nationally representative databases: the 2014 American Community Survey (ACS) and the 2014 County Health Rankings (CHR). County-level data were linked to men diagnosed with EOCRC from SEER by county Federal Information Processing Standards (FIPS) codes [52, 73]. The ACS and CHR comprise nationally representative data from a household sample of the non-institutionalized US population over 18 years of age. The 2014 ACS also provided aggregated estimates for demographic statistics based on the preceding 5-year period (2010-2014). The CHR is a database derived from several survey samples to give generalizable estimates of county-level determinants (e.g., screening practices, job employment, insurance, access to healthy foods; Supplementary Table 4).

From the 2014 ACS, we obtained county-level proportions for age, sex, race/ethnicity (for NH-White and NH-Black), household income, and population with a college education. We also used Rural-Urban Commuting Area (RUCA) codes, which are based on data from the 2010 census and the 2006-2010 ACS [2, 74], for demographic characteristics. Counties were designated as urban or non-urban using the 2010 RUCA classifications [75]. The 11 RUCA codes were then aggregated into a dichotomized variable: (1) Urban (i.e., population centers with 50,000 or more residents) and (2) Non-Urban (i.e., population centers with less than 50,000 residents) [75, 76].

From the 2014 CHR, we included the county-level proportions of adult obesity, smoking, access to exercise opportunities, access to healthy foods, physical inactivity, unemployment, uninsurance, total number of primary care physicians, violent crimes per 100,000 persons, and region as county-level characteristics. We used the US Census definitions of geographic regions (i.e., Midwest, Northeast, South, and West) [76].

Generalized R^2 analysis

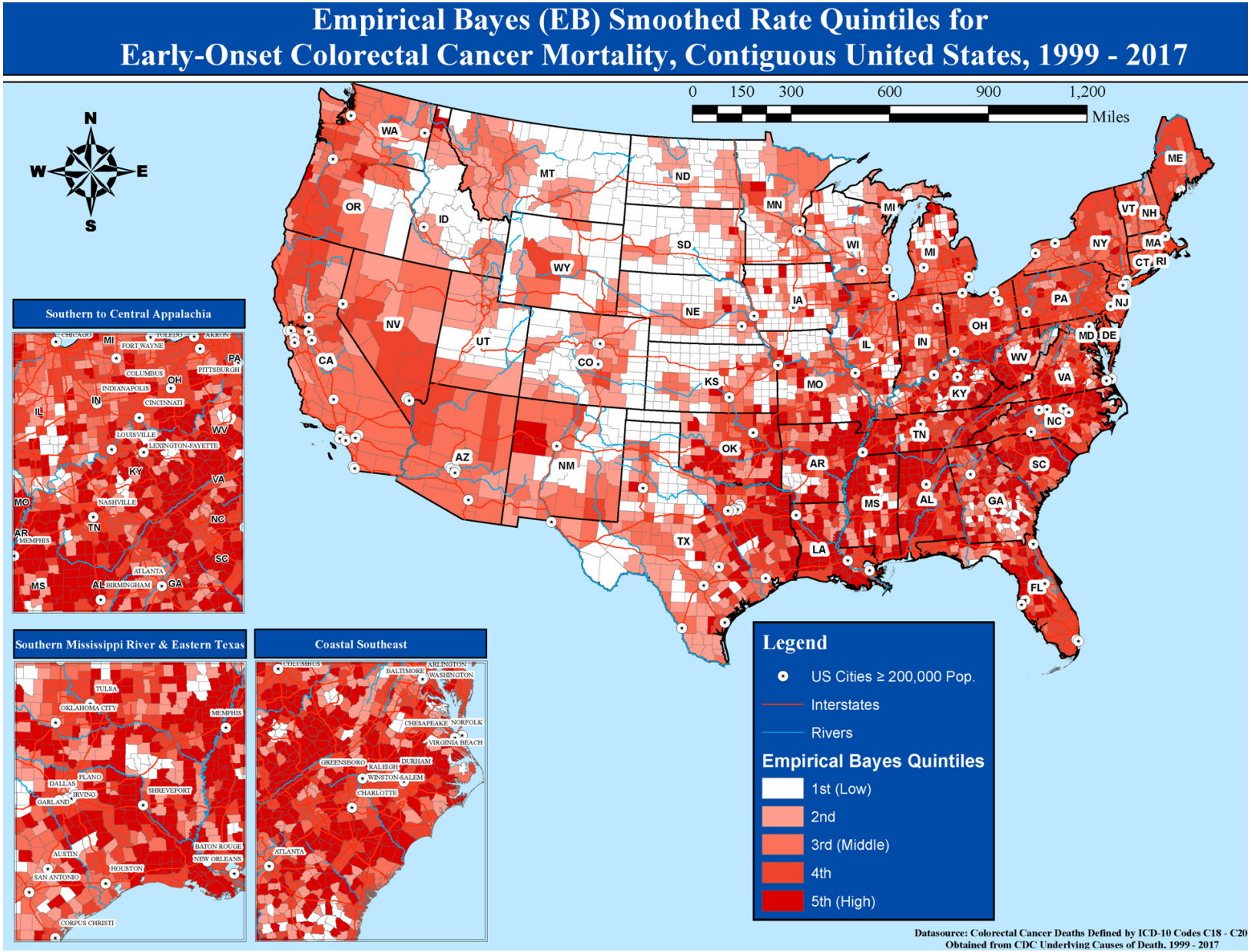
The Cox proportional hazards model developed by Allison [37] and adapted from and based on the Cox and Snell [38] method for the current study followed the equation:

$$R^2_{Allison} = 1 - e^{\left\{\frac{-2[logL(\beta) - logL(0)]}{n}\right\}}$$

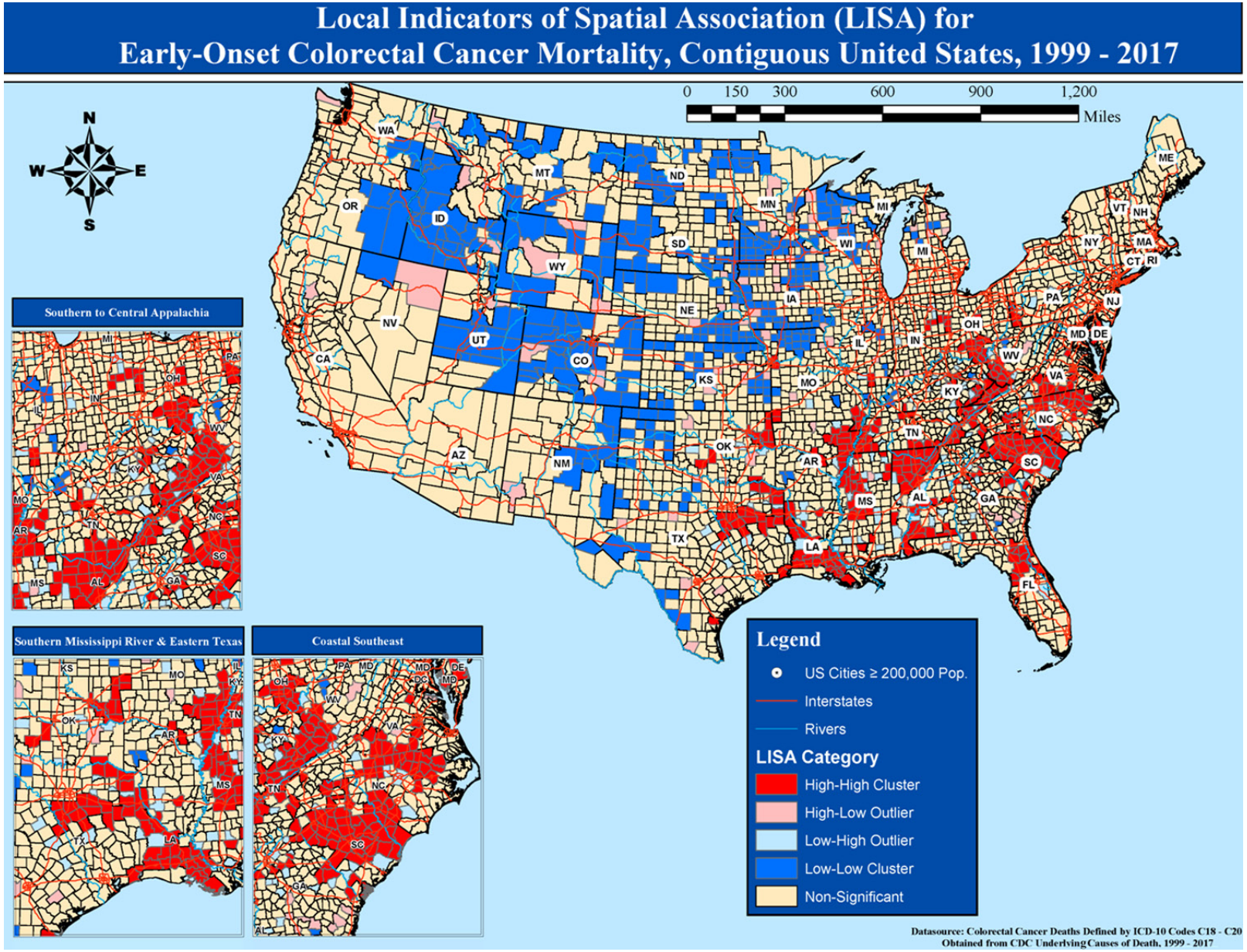
where *L(0)* is the likelihood of the intercept-only model, *L(β)* is the likelihood of the specified model (i.e., model with explanatory variable(s)), and *n* is the sample size. Allison [37] uses the total from the censored summary table (SAS output for PHREG), or the total before censored observations as the *n* for sample size.

Supplementary Table 1. ICD-10 codes for identification of CRC

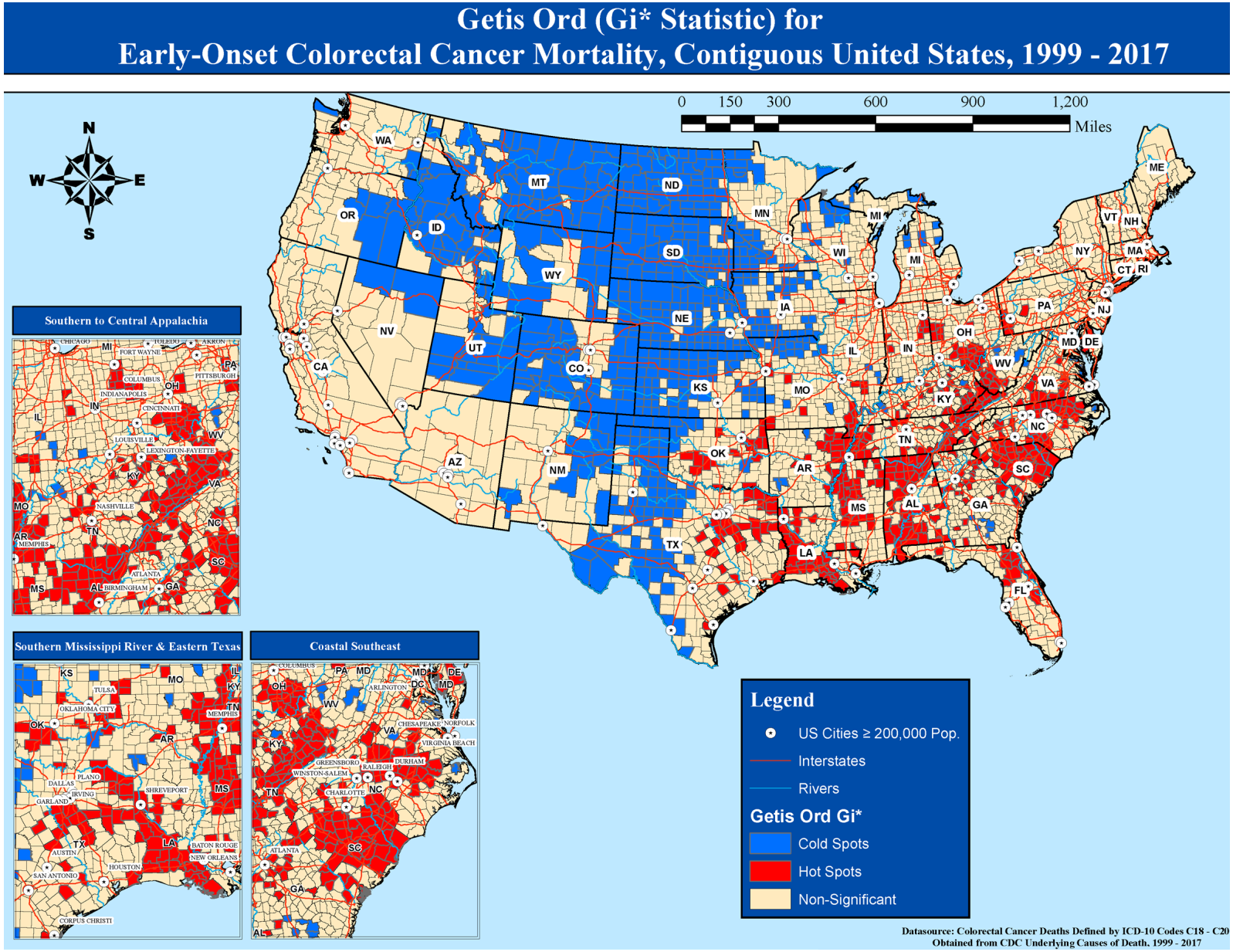
ICD-10 Code	Definition and/or Technical Information
C18.0	Caecum-Malignant neoplasms
C18.1	Appendix-Malignant neoplasms
C18.2	Ascending colon-Malignant neoplasms
C18.3	Hepatic flexure-Malignant neoplasms
C18.4	Transverse colon-Malignant neoplasms
C18.5	Splenic flexure-Malignant neoplasms
C18.6	Descending colon-Malignant neoplasms
C18.7	Sigmoid colon-Malignant neoplasms
C18.8	Overlapping lesion of colon-Malignant neoplasms
C18.9	Colon, unspecified-Malignant neoplasms
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum



Supplementary Figure 1. EOCRC mortality using spatial empirical Bayes smoothed rates quintiles, among all residents in the contiguous United States, 1999-2017.



Supplementary Figure 2. Local indicators of spatial association (LISA) for EOCRC mortality among all residents in the contiguous United States, 1999-2017.



Supplementary Figure 3. Getis-Ord Gi* statistic for EOCRC mortality hotspots among all residents in the contiguous United States, 1999-2017.

Supplementary Table 2. Comparison of early-onset geospatial hotspots[a] by US region, 1999-2017

	Midwest Counties[b] (*N*=1,055)	Northeast Counties[b] (*N*=217)	Southern Counties[b] (*N*=1,422)	Western Counties[b] (*N*=414)	Total (*N*=3108)	*P* Value[c]
	N (%)[d]				*N* (%)[e]	
EOCRC Hotspot[a]	18 (7.76)	0 (0.00)	214 (92.24)	0 (0.00)	232 (7.46)	<.001
LISA High-High Cluster	29 (8.58)	3 (0.89)	306 (90.53)	0 (0.00)	338 (10.88)	<.001
EB 5th Quintile	84 (13.50)	7 (1.13)	526 (84.57)	5 (0.80)	622 (20.01)	<.001
Gi* Hotspot	43 (9.91)	4 (0.92)	387 (89.17)	0 (0.00)	434 (13.96)	<.001

[a]Defined as counties estimated as a hotspot by all 3 geospatial methods (local indicators of spatial association [LISA], empirical Bayes [EB], and Gi*). [b]US regions as determined by the US Census Bureau. Midwest counties are in the states of IN, IL, IA, MI, MN, MO, NE, ND, OH, SD, and WI. Northeast counties are in the states of CT, ME, NH, NJ, NY, PA, RI, and VT. Southern counties are in the states of AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. Western counties are in the states of AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. [c]Significance determined using chi-square test. [d]Denotes row percentages. [e]Denotes column percentages.

Supplementary Table 3. EOCRC mortality hotspot counties and associated rates, 1999-2017

County	FIPS[a]	Region	Crude MR[b]	Age-Adjusted MR	EB Smoothed Rate[c]
Autauga County, AL	01001	South	4.50	4.3419	4.31
Blount County, AL	01009	South	3.41	3.2574	3.83
Choctaw County, AL	01023	South	6.44	-	5.63
Colbert County, AL	01033	South	3.91	3.7477	4.31
Conecuh County, AL	01035	South	6.31	-	4.79
Covington County, AL	01039	South	5.39	4.7964	4.30
Cullman County, AL	01043	South	3.52	3.3131	4.37
Dallas County, AL	01047	South	7.06	6.9882	6.58
Etowah County, AL	01055	South	3.67	3.2929	3.78
Franklin County, AL	01059	South	3.55	-	4.62
Geneva County, AL	01061	South	4.11	-	4.02
Jackson County, AL	01071	South	4.87	4.4408	4.42
Jefferson County, AL	01073	South	3.76	3.6113	3.75
Lauderdale County, AL	01077	South	4.26	3.9599	4.17
Lawrence County, AL	01079	South	5.74	5.1499	4.20
Limestone County, AL	01083	South	3.46	3.2335	3.75
Marion County, AL	01093	South	5.74	5.1372	5.07
Marshall County, AL	01095	South	4.08	3.9081	3.80
Monroe County, AL	01099	South	4.50	-	4.16
Morgan County, AL	01103	South	4.75	4.3453	4.20
Walker County, AL	01127	South	5.06	4.5009	4.03
Winston County, AL	01133	South	5.40	-	4.65
Craighead County, AR	05031	South	3.75	4.1099	4.59
Crittenden County, AR	05035	South	6.22	6.3733	5.08
Cross County, AR	05037	South	5.66	-	5.26
Greene County, AR	05055	South	4.36	4.3322	4.30
Independence County	05063	South	4.01	-	4.14
Jackson County, AR	05067	South	5.82	-	4.27
Lawrence County, AR	05075	South	5.25	-	4.34
Mississippi County, A	05093	South	6.51	6.5995	4.79
Phillips County, AR	05107	South	7.50	7.9873	6.96
Poinsett County, AR	05111	South	4.54	-	4.99
St. Francis County, A	05123	South	4.59	-	4.80

Baker County, FL	12003	South	4.34	-	4.10
Bradford County, FL	12007	South	5.39	-	4.96
Citrus County, FL	12017	South	4.88	3.8562	4.21
Marion County, FL	12083	South	4.27	3.8224	4.11
Putnam County, FL	12107	South	4.28	3.9243	3.75
Sumter County, FL	12119	South	3.92	3.2430	4.05
Union County, FL	12125	South	13.88	12.6491	10.73
Burke County, GA	13033	South	4.70	-	4.46
Dade County, GA	13083	South	7.71	-	4.92
Effingham County, GA	13103	South	3.97	3.9339	3.78
Franklin County, GA	13119	South	5.25	-	4.77
Hart County, GA	13147	South	4.79	-	4.43
Morgan County, GA	13211	South	5.10	-	4.67
Newton County, GA	13217	South	4.30	4.4018	4.10
Richmond County, GA	13245	South	4.32	4.5299	4.22
Franklin County, IL	17055	Midwest	6.19	5.6593	5.62
Blackford County, IN	18009	Midwest	6.37	-	4.30
Jay County, IN	18075	Midwest	6.36	-	4.78
Bell County, KY	21013	South	4.18	-	4.40
Clark County, KY	21049	South	6.08	5.5490	5.03
Garrard County, KY	21079	South	5.28	-	4.30
Greenup County, KY	21089	South	3.35	-	4.08
Harlan County, KY	21095	South	8.58	7.9850	7.85
Knott County, KY	21119	South	6.06	-	6.25
Letcher County, KY	21133	South	9.17	8.1355	7.47
Lincoln County, KY	21137	South	3.89	-	4.09
Montgomery County, KY	21173	South	3.94	-	4.36
Perry County, KY	21193	South	7.35	6.6656	7.18
Pike County, KY	21195	South	7.23	6.3751	6.91
Todd County, KY	21219	South	7.08	-	4.99
Acadia Parish, LA	22001	South	4.90	4.9750	4.47
Allen Parish, LA	22003	South	4.09	-	4.13
Assumption Parish, LA	22007	South	4.96	-	4.68
Beauregard Parish, LA	22011	South	3.74	-	3.78
Caddo Parish, LA	22017	South	4.70	4.6159	4.68
Calcasieu Parish, LA	22019	South	3.84	3.7902	3.87
De Soto Parish, LA	22031	South	5.72	-	4.98
Evangeline Parish, LA	22039	South	6.26	6.6181	4.78
Iberia Parish, LA	22045	South	3.62	3.6515	3.76
Iberville Parish, LA	22047	South	6.97	6.4423	4.60
Jefferson Davis Paris	22053	South	4.50	-	4.17
Natchitoches Parish	22069	South	4.46	5.1701	4.37
Pointe Coupee Parish	22077	South	4.68	-	4.63
Rapides Parish, LA	22079	South	4.60	4.6714	4.53
St. Landry Parish, LA	22097	South	4.73	4.7226	4.42
St. Martin Parish, LA	22099	South	4.39	4.3970	4.36
St. Mary Parish, LA	22101	South	6.02	5.8875	4.79
Terrebonne Parish, LA	22109	South	4.95	4.9577	5.09
Washington Parish, LA	22117	South	3.67	3.5084	3.82
West Baton Rouge Pari	22121	South	3.80	-	3.76
Dorchester County, MD	24019	South	5.05	-	4.20

Attala County, MS	28007	South	8.16	-	7.15
Bolivar County, MS	28011	South	6.52	7.1695	6.20
Carroll County, MS	28015	South	8.67	-	7.11
Coahoma County, MS	28027	South	6.21	6.7602	6.20
Grenada County, MS	28043	South	3.58	-	3.78
Hinds County, MS	28049	South	4.15	4.3898	4.16
Holmes County, MS	28051	South	5.42	-	5.86
Itawamba County, MS	28057	South	4.08	-	4.17
Leake County, MS	28079	South	7.47	7.9794	6.78
Leflore County, MS	28083	South	7.16	8.1354	6.59
Madison County, MS	28089	South	6.11	5.8210	5.72
Monroe County, MS	28095	South	5.82	5.4229	5.42
Quitman County, MS	28119	South	9.87	-	7.14
Scott County, MS	28123	South	5.98	6.0876	5.57
Sunflower County, MS	28133	South	6.58	7.1008	6.08
Tallahatchie County	28135	South	4.95	-	5.38
Yazoo County, MS	28163	South	5.04	-	4.88
Dunklin County, MO	29069	Midwest	4.86	-	5.03
McDonald County, MO	29119	Midwest	4.76	-	3.99
New Madrid County, MO	29143	Midwest	5.18	-	5.05
Newton County, MO	29145	Midwest	4.38	4.1611	3.94
Pemiscot County, MO	29155	Midwest	5.11	-	5.10
Stoddard County, MO	29207	Midwest	6.35	6.0281	5.91
Bertie County, NC	37015	South	6.52	-	5.57
Burke County, NC	37023	South	3.47	3.1096	3.80
Caldwell County, NC	37027	South	4.16	3.7070	3.95
Caswell County, NC	37033	South	6.90	5.5193	5.90
Cleveland County, NC	37045	South	4.32	3.9781	4.23
Edgecombe County, NC	37065	South	6.00	5.6443	5.24
Granville County, NC	37077	South	6.11	5.3252	5.48
Halifax County, NC	37083	South	5.76	5.2568	5.19
Jackson County, NC	37099	SOUTH	4.51	5.2049	4.21
Martin County, NC	37117	South	4.83	-	4.57
Moore County, NC	37125	South	4.73	4.3279	4.01
Nash County, NC	37127	South	4.22	3.8721	3.98
Northampton County, N	37131	South	4.84	-	5.00
Person County, NC	37145	South	5.03	4.4755	4.71
Richmond County, NC	37153	South	5.45	5.1323	4.76
Robeson County, NC	37155	South	4.49	4.7186	4.37
Rockingham County, NC	37157	South	4.65	3.9954	4.28
Scotland County, NC	37165	South	5.00	4.8441	4.72
Vance County, NC	37181	South	6.02	5.8589	5.46
Warren County, NC	37185	South	5.48	-	4.78
Wayne County, NC	37191	South	3.72	3.6688	3.76
Gallia County, OH	39053	Midwest	4.93	-	4.48
Highland County, OH	39071	Midwest	4.09	3.7903	3.99
Jackson County, OH	39079	Midwest	4.07	-	4.18
Lawrence County, OH	39087	Midwest	4.38	4.0602	3.93
Mercer County, OH	39107	Midwest	5.08	4.8461	4.65
Pike County, OH	39131	Midwest	3.05	-	4.02
Ross County, OH	39141	Midwest	4.12	3.7108	3.84

Scioto County, OH	39145	Midwest	3.96	3.8462	4.06
Vinton County, OH	39163	Midwest	5.90	-	4.15
Cherokee County, OK	40021	South	3.83	4.3439	4.39
Choctaw County, OK	40023	South	5.61	-	5.20
Comanche County, OK	40031	South	4.00	4.5712	4.01
Delaware County, OK	40041	South	5.72	5.2051	4.84
Grady County, OK	40051	South	3.98	3.6995	3.88
Muskogee County, OK	40101	South	4.99	4.8449	4.75
Ottawa County, OK	40115	South	4.83	-	4.60
Anderson County, SC	45007	South	4.50	4.1339	4.32
Calhoun County, SC	45017	South	6.05	-	4.47
Cherokee County, SC	45021	South	4.68	4.3684	4.46
Chester County, SC	45023	South	5.73	5.1533	4.93
Clarendon County, SC	45027	South	7.29	6.8520	6.34
Darlington County, SC	45031	South	6.38	6.0001	5.57
Dillon County, SC	45033	South	6.19	6.2055	4.67
Fairfield County, SC	45039	South	5.16	-	4.57
Florence County, SC	45041	South	4.62	4.3622	4.80
Georgetown County, SC	45043	South	4.01	3.5206	3.80
Greenwood County, SC	45047	South	4.83	4.7768	4.91
Hampton County, SC	45049	South	4.80	-	4.10
Horry County, SC	45051	South	4.36	4.0293	4.25
Kershaw County, SC	45055	South	5.52	5.1003	4.93
Lancaster County, SC	45057	South	4.92	4.6185	4.27
Laurens County, SC	45059	South	5.87	5.6856	5.06
Lee County, SC	45061	South	5.99	-	5.07
Marion County, SC	45067	South	3.34	-	4.37
Marlboro County, SC	45069	South	6.48	6.0911	5.17
Newberry County, SC	45071	South	5.69	5.3576	4.80
Oconee County, SC	45073	South	3.92	3.5898	3.93
Orangeburg County, SC	45075	South	5.74	5.6940	5.36
Saluda County, SC	45081	South	4.98	-	3.90
Sumter County, SC	45085	South	4.00	4.0929	4.03
Union County, SC	45087	South	7.09	6.1591	5.33
Williamsburg County	45089	South	6.91	6.3623	6.08
Claiborne County, TN	47025	South	5.65	5.0499	4.57
Dyer County, TN	47045	South	4.58	4.1995	4.59
Fayette County, TN	47047	South	4.13	-	4.02
Franklin County, TN	47051	South	5.20	4.7808	4.63
Gibson County, TN	47053	South	4.17	3.8811	4.01
Giles County, TN	47055	South	5.29	-	4.24
Grainger County, TN	47057	South	5.50	-	4.31
Hamblen County, TN	47063	South	4.45	4.0611	4.70
Hardeman County, TN	47069	South	5.07	-	4.54
Hawkins County, TN	47073	South	5.85	5.1791	4.58
Haywood County, TN	47075	South	4.99	-	4.20
Jefferson County, TN	47089	South	3.25	2.9278	3.81
Knox County, TN	47093	South	3.68	3.5887	3.86
Lauderdale County, TN	47097	South	5.50	5.4041	5.11
Loudon County, TN	47105	South	3.11	-	3.80
McMinn County, TN	47107	South	4.11	3.6514	3.90

Marion County, TN	47115	South	6.07	5.4930	5.14
Meigs County, TN	47121	South	7.12	-	4.00
Monroe County, TN	47123	South	3.62	-	3.93
Polk County, TN	47139	South	5.49	-	3.89
Roane County, TN	47145	South	4.48	3.8158	4.13
Sevier County, TN	47155	South	3.48	3.1577	3.78
Shelby County, TN	47157	South	3.96	3.9992	3.99
Tipton County, TN	47167	South	3.71	3.5932	4.02
Union County, TN	47173	South	4.15	-	3.97
Weakley County, TN	47183	South	4.52	4.5123	4.33
Bowie County, TX	48037	South	4.58	4.3933	4.71
Cass County, TX	48067	South	6.79	6.2488	5.33
Freestone County, TX	48161	South	5.53	-	5.58
Henderson County, TX	48213	South	4.09	3.7462	4.11
Hill County, TX	48217	South	5.15	5.0420	4.10
Jefferson County, TX	48245	South	4.07	3.9446	4.12
Morris County, TX	48343	South	7.92	-	6.40
Navarro County, TX	48349	South	5.03	5.0405	4.35
Orange County, TX	48361	South	4.19	3.9225	4.17
Panola County, TX	48365	South	4.86	-	4.69
Red River County, TX	48387	South	10.06	-	7.42
Rusk County, TX	48401	South	3.84	3.6621	3.86
Bedford County, VA	51019	South	5.07	4.1996	4.78
Brunswick County, VA	51025	South	4.56	-	4.98
Buchanan County, VA	51027	South	6.85	5.6405	6.05
Dickenson County, VA	51051	South	6.20	-	6.16
Dinwiddie County, VA	51053	South	6.38	5.5290	5.46
Halifax County, VA	51083	South	7.64	6.4942	6.60
Lee County, VA	51105	South	5.57	-	5.41
Mecklenburg County, V	51117	South	5.45	4.4714	5.44
Pittsylvania County	51143	South	5.96	4.8137	5.60
Russell County, VA	51167	South	5.40	-	4.65
Scott County, VA	51169	South	4.11	-	4.38
Tazewell County, VA	51185	South	4.71	3.8456	4.68
Wise County, VA	51195	South	4.57	4.1598	5.37
Colonial Heights city	51570	South	4.81	-	4.06
Danville city, VA	51590	South	6.52	5.6819	6.32
Petersburg city, VA	51730	South	7.40	6.9096	6.04
Boone County, WV	54005	South	4.23	-	4.63
Kanawha County, WV	54039	South	4.35	3.7191	4.34
Lincoln County, WV	54043	South	6.25	-	4.30
Logan County, WV	54045	South	5.37	4.4504	5.32
McDowell County, WV	54047	South	5.43	-	5.17
Mingo County, WV	54059	South	5.63	-	5.58
Raleigh County, WV	54081	South	4.49	4.1453	4.41
Wyoming County, WV	54109	South	5.14	-	4.84
Total & mean rates[d]	232 counties		5.20 (4.23-5.93)	4.91 (3.92-5.64)	4.77 (4.13-5.10)

[a]FIPS = Federal Information Processing Standards county codes. [b]MR = mortality rate. Dash (-) indicates counties with unreliable estimate for age-adjusted mortality rate. [c]Spatial empirical Bayes smoothed rate. [d]Overall mean rates presented with 1st and 3rd quartiles.

Supplementary Table 4. Detailed definitions and technical information for 2014 county health rankings (CHR) community characteristics used in study analysis[a]

Community Characteristic	Definition and/or Technical Information
Adult obesity	The proportion of the adult population (aged 20 years and older) that reports a body mass index (BMI) greater than or equal to 30 kg/m^2.
Adult smoking	The proportion of the adult population that currently smokes every day or most days and has smoked at least 100 cigarettes in their lifetime.
Limited access to healthy foods	The proportion of the population that is low income and does not live close to a grocery store. Living close to a grocery store is defined differently in rural and non-rural areas; in rural areas, it means living less than 10 miles from a grocery store; in non-rural areas, less than 1 mile. "Low income" is defined as having an annual family income of less than or equal to 200% of the federal poverty threshold for the family size.
Physical inactivity	The proportion of adults aged 20 years and older reporting no leisure-time physical activity. Examples of physical activities provided include running, calisthenics, golf, gardening, or walking for exercise.
Unemployment	The proportion of the civilian labor force, aged 16 years and older, that is unemployed but seeking work.
Uninsured	The proportion of the population aged 18 to 65 years with no health insurance coverage in a given county.
Primary care physicians per 100,000 persons	The ratio of the population to total primary care physicians. Primary care physicians include non-federal, practicing physicians (MDs and DOs) under age 75 specializing in general practice medicine, family medicine, internal medicine, and pediatrics.
Violent crimes per 100,000 persons	Number of reported violent crime offenses per 100,000 population. High levels of violent crime compromise physical safety and psychological well-being. High crime rates can also deter residents from pursuing healthy behaviors, such as exercising outdoors. Data are obtained by CHR via the Uniform Crime Reporting database.

[a]All variables are county-level proportions.