

Multilevel Small-Area Estimation of Colorectal Cancer Screening in the United States

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Abstract

Background: The U.S. Preventive Services Task Force recommends routine screening for colorectal cancer for adults ages 50 to 75 years. We generated small-area estimates for being current with colorectal cancer screening to examine sociogeographic differences among states and counties. To our knowledge, nationwide county-level estimates for colorectal cancer screening are rarely presented.

Methods: We used county data from the 2014 Behavioral Risk Factor Surveillance System (BRFSS; $n = 251,360$ adults), linked it to the American Community Survey poverty data, and fitted multilevel logistic regression models. We post-stratified the data with the U.S. Census population data to run Monte Carlo simulations. We generated county-level screening prevalence estimates nationally and by race/ethnicity, mapped the estimates, and aggregated them into state and national estimates. We evaluated internal consistency of our modeled state-specific estimates with BRFSS direct state estimates using Spearman correlation coefficients.

Results: Correlation coefficients were ≥ 0.95 , indicating high internal consistency. We observed substantial variations in current colorectal cancer screening estimates among the states and counties within states. State mean estimates ranged from 58.92% in Wyoming to 75.03% in Massachusetts. County mean estimates ranged from 40.11% in Alaska to 79.76% in Florida. Larger county variations were observed in various race/ethnicity groups.

Conclusions: State estimates mask county variations. However, both state and county estimates indicate that the country is far behind the "80% by 2018" target.

Impact: County-modeled estimates help identify variation in colorectal cancer screening prevalence in the United States and guide education and enhanced screening efforts in areas of need, including areas without BRFSS direct-estimates. *Cancer Epidemiol Biomarkers Prev*; 27(3): 245–53. ©2018 AACR.

Introduction

Routine testing for colorectal cancer, starting at age 50 years, saves lives through early detection and removal of precancerous polyps and early-stage cancers. The Centers for Disease Control and Prevention (CDC) reported that in 2014, there were 139,992 new cases of and 51,651 deaths from colorectal cancer (1). A large proportion of premature deaths from colorectal cancer in the United States resulted from racial/ethnic, educational attainment, and geographical inequalities (2). The National Institutes of Health projected in 2010 that medical costs for colorectal cancer are expected to increase with the aging of the U.S. population (3). Nevertheless, in 2012 only 65.1% of adults ages 50 to 75 were current with colorectal cancer screening (4). To reduce the burden of colorectal cancer, the National Colorectal Cancer Roundtable, with the support of the American Cancer Society (ACS) and the CDC, proposed in

2014 a goal of reaching 80% of persons 50 years and older being screened for colorectal cancer by 2018 ("80% by 2018 initiative"; ref. 5). This initiative is now supported by more than 1,000 organizations, including public, private, and voluntary organizations (6).

National health surveys provide reliable estimates of colorectal cancer screening prevalence for the entire United States or for the states (7–9). State-level screening prevalence is often estimated using data from the Behavioral Risk Factor Surveillance System (BRFSS), administered by the CDC (10). The 2012 BRFSS survey revealed large variations among the states in adults ages 50 years and older who were current with screening, with a low of 55.7% in Arkansas and a high of 76.3% in Massachusetts (4). However, a recent study found substantial variation within the state of Missouri, where location (urban versus rural) had a large effect on colorectal cancer screening uptake (11). In addition to geographical location, local communities may show substantial variation in colorectal cancer screening from diversity in social and economic status and demographic and healthcare characteristics, which can be masked when data is aggregated at the state level.

Our goal was to model BRFSS data to provide prevalence estimates of being current with colorectal cancer screening at the county-level nationally and by race/ethnicity, which to our knowledge, are rarely presented. These estimates can potentially help with decisions about local prevention and control plans, and resource allocation. To achieve this goal, we used a model-based small-area estimation (12) that generates county estimates. This method was internally and externally validated (13).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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Materials and Methods

The BRFSS is an annual, state-based, random-digit-dial survey of noninstitutionalized adults aged 18 years or older administered by CDC in collaboration with health departments in the 50 states, District of Columbia, and three territories. Our analysis included only data from the 50 states and the District of Columbia. Trained interviewers in each state collect demographic and health-related information to generate reliable direct estimates of health-risk behaviors, preventive health practices, and access to care through landline or cell phone interviews. The 2014 survey combined landline and cell phone response rates, which ranged from 25.1% in California to 60.1% in South Dakota, with a median rate of 47%. Detailed information about the response rate can be found on the BRFSS website (10). We poststratified the sampled population of the 2014 BRFSS data with the U.S. Census 2010 population counts at the county level (14) to improve the information about the sampled population. The U.S. Census provides detailed information about each county's 2014 population, by age (5-year age groups from ages 50 to 74), sex, race/ethnicity [8 non-Hispanic (NH) and Hispanic or Latino origin groups: NH white, NH black, NH American Indian or Alaska Native, NH Asian, NH Native Hawaiian or other Pacific Islander, NH other single race, NH 2 or more races; or Hispanic]. This information about adults age 75 years was obtained from the National Center for Health Statistics (15). County-level poverty rates ($\leq 150\%$ of the federal poverty rate), which are associated with colorectal cancer (16, 17), were extracted from the American Community Survey (ACS) 2010–2014 (18). Additional information included respondent county ($n = 3,142$ counties) and state ($n = 51$; 50 states and the District of Columbia) identifiers.

Colorectal cancer screening test use

Because the latest BRFSS data available for analysis in our study was from 2014, we followed the 2008 USPSTF colorectal cancer screening guideline recommendations in effect at that time to routinely screen average risk adults ages 50–75 years, with one of three options: (i) fecal occult blood testing (FOBT) within 1 year, or (ii) sigmoidoscopy within 5 years with FOBT within 3 years, or (iii) colonoscopy within 10 years (19).

Respondents ages 50 years and older were asked 5 questions to assess colorectal cancer test use including blood stool test, sigmoidoscopy, and colonoscopy. Each of the tests was described to help the respondent identify the test. The BRFSS questions did not include details about the indication for the test (i.e., for screening or for diagnosis/treatment purposes). As a result, the BRFSS questions are best considered a general measure of test use rather than a specific measure of screening.

The BRFSS described blood stool test (fecal occult blood test, or FOBT) as a test that may use a special kit at home to determine whether the stool contains blood. Sigmoidoscopy and colonoscopy were described as exams in which a tube is inserted in the rectum to view the colon for signs of cancer or other health problems. Respondents were asked whether they had had any of the three tests. Those who answered "yes" were further asked how long it had been since their most recent test.

Following the USPSTF recommendations, we defined colorectal cancer screening status for any colorectal cancer screening test for adults ages 50 to 75 years as follows:

Current: Respondents tested for at least one of the three test types according to recommendations.

Not current: Respondents who had at least one of the tests, but no test was within the recommended time interval, or those who had never had any of the three tests.

The outcome of being current with any colorectal cancer test type is used as a measure for comparing adherence with the 80% by 2018 goal. Additional analyses for colonoscopy and FOBT are to assess what is being practiced in reality and how the reported use of each test type is distributed at the county level.

Statistical analysis

We used the 2014 BRFSS individual-level county data (sample size = 251,360 adults) and linked it with the ACS to construct and fit three multilevel logistic regression mixed models that estimated the expected probability of an individual being "current" with any colorectal cancer test use; with colonoscopy; and with FOBT, in each county in the United States. Each model included individual-level fixed effects (age, sex, race/ethnicity), county-level poverty, and county- and state-level random effects. The results from each of the three models included parameters for each of the fixed and random variables.

Because some BRFSS counties had no direct estimates and no random effects, we defined a county-level random effect μ_c^i for any county-level i with a missing random effect, by spatially smoothing its adjacent counties' random effects μ_c^j ($j \neq i$) and averaging them. We then linked the newly created random effects back to the county random effects list. We post-stratified the BRFSS data with U.S. Census county population counts and used them with the updated random effect list and the estimated parameters from each model in newly constructed Monte Carlo simulation programs. Each simulation included 1,000 randomly drawn samples for each of the parameters and their standard errors, to predict the individual-level expected probability of being current with the respective colorectal cancer screening type. Our choice of a flexible spatial smoothing method was driven by caution about over-smoothing health behavior outcome variations in adjacent counties and by BRFSS data, where direct estimate calculations for some counties were limited (20, 21). We did not present county estimates for the option of sigmoidoscopy every 5 years with FOBT every 3 years because of small percentages.

Additional analysis included county-level models to generate estimates by race/ethnicity for being current with any colorectal cancer test type.

Our multilevel logistic regression models followed the generalized linear mixed models general formula (12):

$$P_{ijkcs}(y_{ijkcs} = 1) = \text{logit}^{-1}(\alpha_i + \beta_j + \gamma_k + x'_c \eta + \mu_c + \nu_s),$$

y_{ijkcs} is the self-reported screening status (1 = current, 0 = not current or never been screened) for an individual in age group i , $i = 1$ to 6, sex group j , $j = 1$ to 2, and race/ethnicity group k , $k = 1$ to 8, from county c in state s , and their respective regression coefficients. x_c is a vector of county-level covariates and η is a vector of their respective regression coefficients. The prediction

model included a product of the county-level poverty status x'_c and its respective regression coefficient η . μ_c and ν_s are the county- and state-level random effects, which were assumed to be independent and normally distributed.

We used the results from the generated respective samples of 1000 SAEs to summarize the prevalence estimates for each of the three screening types by county, by state, and for the entire United States and generated predicted mean values, their standard errors, and 95% confidence intervals (CIs). The prevalence estimates calculations are described below:

For example, P^1_{cs} is the county-level estimated prevalence of being current with any test use in county c within state s , P_{ijkcs} is the individual probability of being in age group i , sex group j , and race/ethnicity group k , in county c and state s , Pop_{ijkcs} is the respective population count, and Pop_{cs} is the total population count in county c within state s ,

$$\begin{aligned} \text{then } P^1_{cs} &= \left[\sum_i \sum_j \sum_k (P_{ijkcs} \times \text{Pop}_{ijkcs}) \right] / \sum_i \sum_j \sum_k (\text{Pop}_{ijkcs}) \\ &= \left[\sum_i \sum_j \sum_k (P_{ijkcs} \times \text{Pop}_{ijkcs}) \right] / \text{Pop}_{cs}. \end{aligned}$$

Similarly, let P^2_{cs} = the county-level prevalence of not being current with colorectal cancer screening or never been screened for colorectal cancer in county c within state s ,

$$\text{then } P^2_{cs} = \left[\sum_i \sum_j \sum_k ((1 - P_{ijkcs}) \times \text{Pop}_{ijkcs}) \right] / \text{Pop}_{cs}.$$

The above prevalence calculations utilize the county population counts from the Census as weights.

We calculated summary statistics for the model-based county distributions (total and by race/ethnicity) with the univariate procedure. We also calculated direct estimates (means and 95% CIs) by race/ethnicity with the BRFSS data. For race/ethnicity analysis, we combined NH Native Hawaiian or other Pacific Islander with NH other single race and NH 2 or more races. Summary statistics for state estimates for both the 2014 BRFSS direct estimates and our model-based SAE estimates were calculated with the MEANS procedure.

We validated internal consistency between the BRFSS and the model-based state estimates and estimates of counties with 500 or more respondents with the Spearman correlation coefficients and mean absolute differences between the estimates. In addition, we used ArcGIS (Esri) to separately map the model-based county estimates for each of the estimated percentages of being current with any colorectal cancer screening test, with colonoscopy, and with FOBT. Summary statistics by race/ethnicity were only compared with reliable BRFSS direct-estimates such as means and medians. We used the SAS GLIMMIX procedure (SAS Institute Inc.) to fit the BRFSS multilevel logistic models with unweighted data, based on a validation study showing that an unweighted model generated more accurate small area estimates (13). The multilevel simulation models were fitted with SAS Version 9.3. BRFSS states summary estimates calculations for internal consistency were performed with SAS-callable SUDAAN (Research Triangle Institute, Research Triangle Park, NC).

Results

Our 2014 BRFSS analytic file included information from a sample of 251,360 adults 50 to 75 years old. Our post-stratification included current U.S. Census 2010 population data from all 3,142 U.S. counties. The national 2014 model-based SAE prevalence estimate for being current with colorectal cancer screening was 67.28%, 95% CI, (66.83–67.71%) whereas the direct 2014 BRFSS estimate was 66.24%, 95% CI (65.83–66.65%; Table 1). Mean national estimates for the race/ethnicity groups ranged from 69.16% for NH white to 56.81% for Hispanic, with county estimates being lower by 1% to 5% except for NH AIAN, where the national and county means were similar. The overall ranges of county estimates were between 34.45% for NH white and 47.76% among NH Asians, indicating a large variability. BRFSS mean estimates were very similar to the model-based means with 66.24% for the national estimate, 68.33% for NH white, 67.79% for NH black, and somewhat lower (50.82%) for Hispanic.

Our national model-based SAE prevalence estimate for colonoscopy within the past 10 years was 63.69%, and was 9.67% for FOBT within the past year. BRFSS estimates were 62.48% and 9.86%, respectively (Table 1).

The Spearman correlation coefficients (CC) between our state-level model-based SAE estimates and BRFSS direct estimates was 0.95 for being current with any colorectal cancer test type, 0.96 for colonoscopy, and 0.97 for FOBT (Table 2). Spearman CC for county estimates with ≥ 500 respondents was 0.86 for being current with any colorectal cancer test type (Pearson CC was 0.9).

Except for NH white, state model-based summary statistics for the remaining race/ethnicity groups show a much larger spread for the BRFSS estimates with interquartile estimates ranging from 10.96% to 18.85%. In contrast, the model-based estimates range from 5.68% to 8.51%.

Table 3 presents the model-based estimated prevalence for being current with any colorectal cancer test type by state in ranked order and for FOBT, and county estimates (%) summarized by state. Figure 1 presents county estimated prevalence (%) for being current with colorectal cancer screening by any colorectal cancer test, colonoscopy and FOBT.

Being current with any colorectal cancer test type

Model-based states estimated prevalence ranged from 58.92% in Wyoming to 75.03% in Massachusetts with a mean of 67.11% and a median of 67.47% (Tables 2 and 3). States with the highest prevalence ($>70\%$) were in the Northeast (Massachusetts, Maine, Rhode Island, Connecticut, New Hampshire, and Vermont), Midwest (Michigan, Minnesota, Wisconsin), South (Delaware, Maryland, District of Columbia, North Carolina), and West (Washington; Table 3). States with the lowest prevalence ($<62\%$) included Wyoming, Oklahoma, New Mexico, Alaska, Idaho, and Arkansas (Table 3). The overall range (minimum to maximum) of the county estimates within the states was lowest in Connecticut (3.60%), indicating low variability among these counties, and highest in South Dakota (28.61%) with Texas, Alaska, North Dakota, and New Mexico, each having a range $>20\%$, indicating a high variability.

SAE county prevalence estimates ranged from 40.11% in Alaska to 79.76% in Florida with a median of 65.53% (Tables 1

Table 1. Model-based SAE summary statistics (%) for being current with colorectal cancer screening overall, by county, and by race/ethnicity and comparison with the mean (%) and 95% CI for BRFSS select race/ethnicity groups

Test	No. of counties	Mean (95% CI)	Min	Lower quartile	Median	Upper quartile	Max	Interquartile range	Overall range	BRFSS mean (95% CI)
Any colorectal cancer test type										
Overall										
U.S.		67.28 (66.83–67.71)								66.24 (65.83–66.65)
Counties	3142	65.23	40.11	62.04	65.53	68.88	79.76	6.84	39.65	
NH white										
U.S.		69.16 (68.77–69.55)								68.33 (67.92–68.73)
Counties	3142	66.29	45.96	63.17	66.41	69.72	80.41	6.54	34.45	
NH black										
U.S.		67.69 (67.17–68.17)								67.79 (66.42–69.12)
Counties	3065	64.07	33.09	60.64	64.87	68.32	80.79	7.68	47.70	
NH AIAN ^a										
U.S.		57.81 (57.19–58.41)								
Counties	3110	58.24	30.01	54.28	58.55	62.60	75.36	8.32	45.35	
NH Asian										
U.S.		61.99 (60.88–63.00)								
Counties	3075	56.90	28.67	52.43	56.89	61.03	75.43	8.60	47.76	
NH other ^b										
U.S.		63.12 (62.44–63.76)								
Counties	3127	60.27	34.29	57.02	60.71	64.08	75.22	7.06	40.96	
Hispanic										
U.S.		56.81 (55.82–57.71)								50.82 (48.79–52.85)
Counties	3134	53.34	25.05	49.76	53.53	57.22	71.00	7.45	45.95	
Colonoscopy										
Overall										
U.S.		63.69 (63.20–64.16)								62.48 (62.06–62.90)
Counties	3142	62.01	35.36	58.65	62.23	65.76	76.73	7.11	41.36	
FOBT										
Overall										
U.S.		9.67 (9.43–9.90)								9.86 (9.59–10.14)
Counties	3142	8.47	3.28	7.29	8.19	9.34	20.54	2.05	17.26	

NOTE: SAE, small area estimates.

Any colorectal cancer test type = home FOBT within the past year; sigmoidoscopy within 5 years with FOBT within 3 years; or colonoscopy within 10 years. We used a modified Monte Carlo simulation method for estimating the model-based predicted standard errors.

^aAIAN = American Indian/Alaska Native.^bNH other = Pacific Islander (PI), other one race, and 2 or more races.An additional analysis comparing mean estimates of counties with ≥ 500 respondents shows that the mean abs difference between the model-based estimates and the BRFSS direct estimates for being current with any colorectal cancer test type is 2.3, SE = 0.127 and interquartile range = 2.43.

and 3; Fig. 1a). The lowest ranking counties ($\leq 49.50\%$) were in Alaska, South Dakota, North Dakota, Texas, Idaho, Montana, and Arizona. Counties with estimated prevalence of 75% or more ($n = 31$) were in the Northeast (Rhode Island, Massachusetts, Maine, and Connecticut), Midwest (Michigan, Wisconsin), South (Florida, Virginia, Maryland, and Delaware), and the West (California, Washington; Table 3; Fig. 1A). Additional details about the 20 counties with the highest and lowest percentages and the predicted standard errors of county estimates for being current with any colorectal cancer test type are presented in the supplementary data in Supplementary Table S1 and Supplementary Fig. S1.

Being current with colonoscopy

Model-based state-estimated prevalence ranged from 56.16% in Oklahoma to 72.02% in Maine with a mean of 64.00% and a median of 64.26% (Table 2). States with the highest prevalence ($\geq 70\%$) were in the Northeast (Maine, Rhode Island, Massachusetts, Connecticut, and New Hampshire) and Delaware. States with the lowest ranking percentages ($\leq 60\%$) included Oklahoma, Wyoming, New Mexico, Hawaii, Nevada, Alaska, Arkansas, Idaho, Texas, Nebraska, Mississippi, and California.

County prevalence estimates ranged from 35.36% in Alaska to 76.73% in Rhode Island with a mean of 62.01% and a median of 62.23% (Table 1; Fig. 1b). The 20 lowest ranking counties (≤ 44.61) were in Alaska, South Dakota, North Dakota, New Mexico, Texas, Idaho, Arizona, Montana, and Nebraska. Counties with the highest prevalence ($\geq 73\%$, $n = 20$) were in the Northeast (Rhode Island, Maine, Massachusetts, and Connecticut), Midwest (Michigan, Wisconsin, and Minnesota), and South (Florida and Virginia).

Being current with FOBT

Model-based state estimated prevalence ranged from 3.73% in Utah to 16.83% in California with a mean of 8.49% and a median of 8.21% (Table 2). States with the highest prevalence ($\geq 11\%$) included California, Hawaii, Florida, and Nevada. The lowest ranking states ($< 6\%$) included Utah, Wyoming, Alaska, and Minnesota (Table 3).

County prevalence estimates ranged from 3.28% in Utah to 20.54% in California (Table 3; Fig. 1C), with a mean of 8.47% and a median of 8.19% (Table 1). Most counties with the lowest prevalence ($\leq 5.19\%$, $n = 34$) were in Utah, Wyoming, and Alaska. Counties with the highest prevalence ($\geq 16\%$, $n = 30$) were in California and Hawaii.

Table 2. State ($n = 51$) summary statistics (%) for being current with colorectal cancer screening by screening type and race/ethnicity—model-based SAE versus 2014 BRFSS

Test	ρ^a	Mean	Min	Lower quartile	Median	Upper quartile	Max	Interquartile range
Any colorectal cancer test type								
All								
Model-based	0.95	67.11	58.92	63.00	67.47	70.38	75.03	7.38
BRFSS		66.24	56.52	61.81	66.35	69.95	76.37	8.15
NH white								
Model-based		68.56	59.87	60.64	64.87	71.76	76.13	6.24
BRFSS		67.82	56.99	64.63	67.58	71.87	78.03	7.24
NH black								
Model-based		67.08	58.51	64.54	66.81	70.23	74.58	5.68
BRFSS ^b		64.71	34.37	60.29	65.61	71.25	86.83	10.96
NH AIAN ^c								
Model-based		59.50	47.23	55.23	59.80	63.75	69.04	8.51
BRFSS		57.70	30.77	49.84	57.67	64.38	79.25	14.54
NH Asian								
Model-based		59.70	50.19	56.76	59.77	63.41	67.87	6.66
BRFSS ^d		54.88	14.59	45.90	56.39	64.30	89.76	18.40
NH other ^e								
Model-based		62.05	53.41	58.65	61.59	65.30	70.20	6.61
BRFSS		61.29	32.13	54.76	62.78	68.62	80.52	13.86
Hispanic								
Model-based		55.76	46.96	52.18	55.75	59.48	65.02	7.30
BRFSS		52.47	26.63	43.66	52.26	62.51	82.35	18.85
Colonoscopy								
Model-based	0.96	64.00	56.16	60.15	64.26	67.73	72.02	7.58
BRFSS		62.94	53.81	58.57	62.50	67.11	73.06	8.54
FOBT								
Model-based	0.97	8.49	3.73	7.06	8.21	9.97	16.83	2.91
BRFSS		8.53	2.86	6.62	7.93	10.13	20.54	3.52

NOTE: NH, non-Hispanic.

Any colorectal cancer test type = home FOBT within the past year; sigmoidoscopy within 5 years with FOBT within 3 years; or colonoscopy within 10 years; SAE, small area estimates; BRFSS, behavioral risk factor surveillance system.

ρ^a = The Spearman correlation coefficients. The correlation coefficient test was performed for the overall national estimates only. Because the BRFSS is a state-based survey and did not include data for all counties, the race groups were not assessed with correlation coefficients. The similarity between the SAE and BRFSS distributions was assessed by comparing the means and the medians.

The mean abs difference between the model-based state-estimates and the BRFSS direct state-estimates for each colorectal cancer screening type is as follows: (i) Any colorectal cancer test type: mean = 1.36%, SE = 0.14; (ii) colonoscopy: mean = 1.5%, SE = 0.161; and (iii) FOBT: Mean = 0.608%, SE = 0.088.

^bWe excluded one state with a minimum estimate = 0.0.

^cAIAN = American Indian/Alaska Native.

^dWe excluded one state with a maximum estimate = 100.0.

^eNH other = Pacific Islander (PI), other one race, and 2 or more races.

Discussion

We present results from a small area estimation model, which generated 3,142 county estimates nationally for being current with any colorectal cancer test type, with colonoscopy, and with FOBT. In addition, we presented model-based county estimates for being current with any colorectal cancer test type by race/ethnicity groups and by mean estimates of counties with ≥ 500 respondents. Our nationwide, race/ethnicity-specific modeled estimates were consistent with BRFSS direct estimates. These estimates can potentially provide useful information at the local and state levels and can inform decisions about resource allocation to geographically targeted prevention and control plans to increase colorectal cancer screening. Our study shows, that in 2014, most states and counties in the United States were still far from the "80% by 2018 initiative" target.

We found substantial geographic variation in the estimated prevalence of current colorectal cancer screening across states and among counties within states. Consistent with a previous study (4), the highest ranking state estimates of being current with any colorectal cancer test type were in the Northeast.

The lowest ranking state estimates were in various regions of the West, South, and Alaska, some of which were also observed previously for their low estimated percentages (4). Estimated percentages for FOBT were much lower, and varied among states.

Differences in estimated percentages between the highest and lowest ranking counties were approximately 40% for any colorectal cancer test type or for colonoscopy. The highest-ranking counties were most often in the Northeast with 70% or more of their counties being current with colorectal cancer screening. The lowest ranking counties were in the rural areas of Alaska, North Dakota, South Dakota, New Mexico, and Montana, where a large proportion of their populations were American Indians (22), had income below the poverty rate or had low education attainment. Other low-ranking counties were in Texas, some of which had a large Hispanic or Latino population (23), had low income or low education. The aforementioned states had the largest county variations in current colorectal cancer screening, which might indicate disparities in access to care between rural and metropolitan

Table 3. Model-based SAE state estimated mean (%) and county statistics summarized by state for being current with any colorectal cancer test type and with FOBT screening

State	State mean ^a	Any colorectal cancer test type							FOBT							
		County summary statistic							County summary statistic							
		Min	Q1	Mean	Median	Q3	Max	Range	State mean	Min	Q1	Mean	Median	Q3	Max	Range
Massachusetts	75.03	72.35	73.85	74.92	74.92	75.90	77.79	5.44	10.02	9.04	9.35	9.32	9.68	10.35	12.43	3.38
Maine	74.34	69.61	72.38	73.68	73.88	75.13	76.95	7.34	7.03	5.84	7.01	7.37	7.37	7.85	8.85	3.01
Rhode Island	74.18	71.47	76.47	76.29	77.18	77.40	78.92	7.44	8.22	7.95	8.05	8.32	8.14	8.60	8.85	0.90
Connecticut	73.11	71.94	72.78	73.83	74.00	74.80	75.55	3.60	8.54	7.63	7.92	8.35	8.21	8.80	9.31	1.68
Delaware	72.81	71.42	71.42	73.30	73.27	75.22	75.22	3.80	6.40	5.70	7.70	6.69	6.94	7.41	7.41	1.71
New Hampshire	72.40	67.14	71.08	71.72	71.59	73.58	73.97	6.83	6.49	5.99	6.27	6.72	6.64	6.87	8.26	2.28
Maryland	72.25	66.19	70.07	71.41	71.60	73.24	75.22	9.03	10.62	7.67	9.44	10.16	10.07	11.04	12.42	4.76
Washington, DC	72.17			72.17					10.67			10.67				
Michigan	71.83	67.56	71.19	72.39	72.37	73.68	76.78	9.22	8.63	7.29	8.39	8.64	8.57	8.90	10.94	3.65
Minnesota	71.38	63.23	70.13	71.10	71.56	72.19	74.63	11.39	5.80	5.23	5.79	5.96	5.92	6.06	7.51	2.28
North Carolina	70.60	62.47	68.61	70.19	70.33	71.46	74.83	12.36	10.55	8.96	10.29	10.76	10.68	11.23	12.48	3.52
Vermont	70.47	64.82	68.60	69.96	69.81	71.57	73.41	8.60	6.79	5.52	6.48	7.18	7.06	7.80	9.29	3.77
Wisconsin	70.38	59.11	69.54	70.41	70.64	71.58	75.64	16.53	6.40	5.81	6.39	6.63	6.56	6.79	9.89	4.09
Washington	70.19	58.46	67.86	69.19	69.40	71.27	75.07	16.61	10.26	8.88	9.78	10.28	10.16	10.74	12.35	3.48
Florida	69.63	59.83	67.80	69.62	70.02	71.33	79.76	19.94	13.17	10.69	12.36	12.84	12.69	13.23	15.60	4.91
Virginia	69.57	58.78	66.69	68.68	69.18	70.80	75.61	16.83	7.39	6.36	7.24	7.51	7.46	7.75	8.79	2.43
Utah	69.27	53.35	65.78	66.79	66.94	68.96	72.84	19.50	3.73	3.28	3.94	4.12	4.11	4.29	5.33	2.04
Oregon	68.92	61.78	66.53	68.07	68.12	69.70	72.04	10.26	10.01	8.72	9.43	9.70	9.65	9.96	11.13	2.42
South Carolina	68.85	61.44	65.40	67.19	67.21	69.39	74.37	12.93	7.80	6.84	7.57	7.97	8.06	8.36	9.14	2.3
Kentucky	68.40	57.26	64.64	66.74	66.95	69.04	73.78	16.52	9.56	8.59	9.33	9.64	9.56	0.86	12.23	3.65
Georgia	68.06	58.25	64.84	66.92	66.86	68.65	74.31	16.07	9.97	8.83	9.64	10.00	10.00	10.34	11.40	2.57
Iowa	67.71	62.26	66.56	67.47	67.38	68.53	71.08	8.82	7.27	6.45	7.10	7.29	7.25	7.46	8.51	2.06
California	67.68	58.10	67.39	69.33	69.95	72.17	75.55	17.45	16.83	14.46	15.81	16.49	16.25	16.76	20.54	6.08
New York	67.61	60.91	68.22	69.22	69.45	70.55	73.83	12.93	8.30	7.44	8.06	8.20	8.19	8.31	9.04	1.60
South Dakota	67.58	43.80	64.93	65.84	68.21	69.32	72.41	28.61	8.21	6.47	7.90	8.55	8.14	8.56	12.72	6.25
Pennsylvania	67.47	64.50	66.42	67.51	67.48	68.59	71.63	7.14	7.45	6.59	7.22	7.49	7.53	7.74	8.34	1.75
Alabama	67.09	58.23	63.82	65.29	65.33	66.80	70.80	12.57	8.28	7.58	8.01	8.51	8.53	8.88	9.98	2.40
Tennessee	67.01	60.20	64.43	65.81	65.59	67.01	71.76	11.56	9.22	8.28	8.94	9.15	9.10	9.32	10.89	2.61
Hawaii	66.78	61.23	64.40	64.60	64.42	64.96	68.00	6.75	15.33	11.67	14.80	15.87	15.05	18.69	19.12	7.44
Colorado	66.62	53.28	61.55	63.57	63.89	66.52	70.38	17.10	8.32	6.92	7.88	8.13	8.09	8.38	10.43	3.51
Kansas	66.43	54.33	62.68	64.25	64.70	66.15	71.81	17.48	8.10	6.53	8.21	8.39	8.38	8.61	9.40	2.88
West Virginia	66.20	57.80	63.98	65.20	65.41	66.46	70.18	12.38	9.55	8.62	9.29	9.62	9.57	9.96	10.66	2.04
Louisiana	65.73	54.02	63.03	64.35	64.30	65.99	69.11	15.09	9.45	8.26	9.06	9.42	9.47	9.78	11.00	2.74
Arizona	65.57	49.44	56.89	60.43	60.34	66.32	68.55	19.11	10.72	8.35	8.92	10.35	9.78	11.68	14.16	5.81
Ohio	65.17	58.75	63.06	64.17	64.32	65.38	70.09	11.34	7.75	6.88	7.31	7.56	7.51	7.72	9.08	2.20
New Jersey	65.15	56.36	63.11	65.18	66.54	67.22	68.97	12.61	7.71	6.67	7.31	7.69	7.73	8.11	8.82	2.15
Missouri	63.96	55.83	59.58	61.61	61.47	63.32	68.62	12.79	7.11	6.32	7.23	7.36	7.36	7.53	8.18	1.85
Mississippi	63.37	52.84	60.46	61.92	62.32	63.86	69.09	16.25	10.63	9.45	10.35	10.82	10.74	11.34	12.15	2.70
North Dakota	63.00	43.73	59.95	60.98	62.07	63.13	68.19	24.46	7.06	5.69	7.05	7.38	7.23	7.54	10.42	4.73
Texas	62.93	45.14	61.27	62.87	63.90	65.79	71.80	26.66	8.56	7.16	8.42	8.63	8.64	8.81	10.51	3.34
Montana	62.86	48.85	59.48	61.10	61.81	63.43	66.38	17.53	6.53	5.75	6.48	6.77	6.66	6.84	9.57	3.82
Indiana	62.84	52.65	61.16	62.95	62.67	64.54	69.68	17.03	7.90	7.01	7.62	7.80	7.76	7.93	9.46	2.45
Nevada	62.62	54.64	60.30	61.07	61.66	62.54	65.82	11.18	11.01	7.64	8.45	9.09	8.79	9.30	12.20	4.56
Nebraska	62.42	49.57	57.90	59.45	59.20	61.18	65.38	15.80	7.17	5.64	6.90	7.23	7.20	7.44	9.68	4.03
Illinois	62.12	51.78	60.97	62.11	62.29	63.26	66.71	14.93	6.36	5.60	6.24	6.34	6.33	6.44	7.07	1.47
Arkansas	61.74	50.96	58.57	60.04	60.11	61.73	69.16	18.20	7.18	6.67	7.07	7.37	7.37	7.58	8.27	1.60
Idaho	61.43	46.46	57.47	59.13	59.32	61.23	66.01	19.55	6.31	5.55	6.23	6.45	6.42	6.58	7.73	2.18
Alaska	60.75	40.11	52.14	56.60	59.12	60.98	66.29	26.17	5.50	4.83	5.46	6.28	5.83	7.06	8.56	3.73
New Mexico	60.71	45.96	54.85	57.63	57.18	61.20	69.80	23.85	7.53	6.24	7.22	7.47	7.40	7.65	10.59	4.35
Oklahoma	59.27	50.13	55.50	57.45	57.62	59.09	63.61	13.49	8.22	6.94	7.58	8.01	7.92	8.37	10.09	3.15
Wyoming	58.92	52.03	56.38	58.33	58.02	60.64	63.84	11.81	5.35	4.35	5.29	5.54	5.59	5.76	6.73	2.38

NOTE: Q1, lower quartile; Q3, upper quartile.

Any colorectal cancer test type = FOBT within the past year; sigmoidoscopy within 5 years with FOBT within 3 years; or colonoscopy within 10 years.

^aPercentages are in decreasing order of state prevalence of being current with any colorectal cancer test option. Percentages for FOBT match by state.Ranges with percentages $\geq 15\%$ are highlighted.

areas. Moreover, our model-based county estimates by race/ethnicity suggest even larger disparities among non-Hispanic blacks, Asians, American Indians or Alaska Natives, and Hispanics, for whom culturally appropriate interventions are needed. We were not able to compare estimates for these subpopulation groups with BRFSS estimates because BRFSS

is a state-level survey and is not designed to assess county reliability for these populations solely. Comparing county-level data with BRFSS can be potentially biased because of oversampling or having counties without BRFSS direct estimates. Nevertheless, the mean and median estimates were consistent.

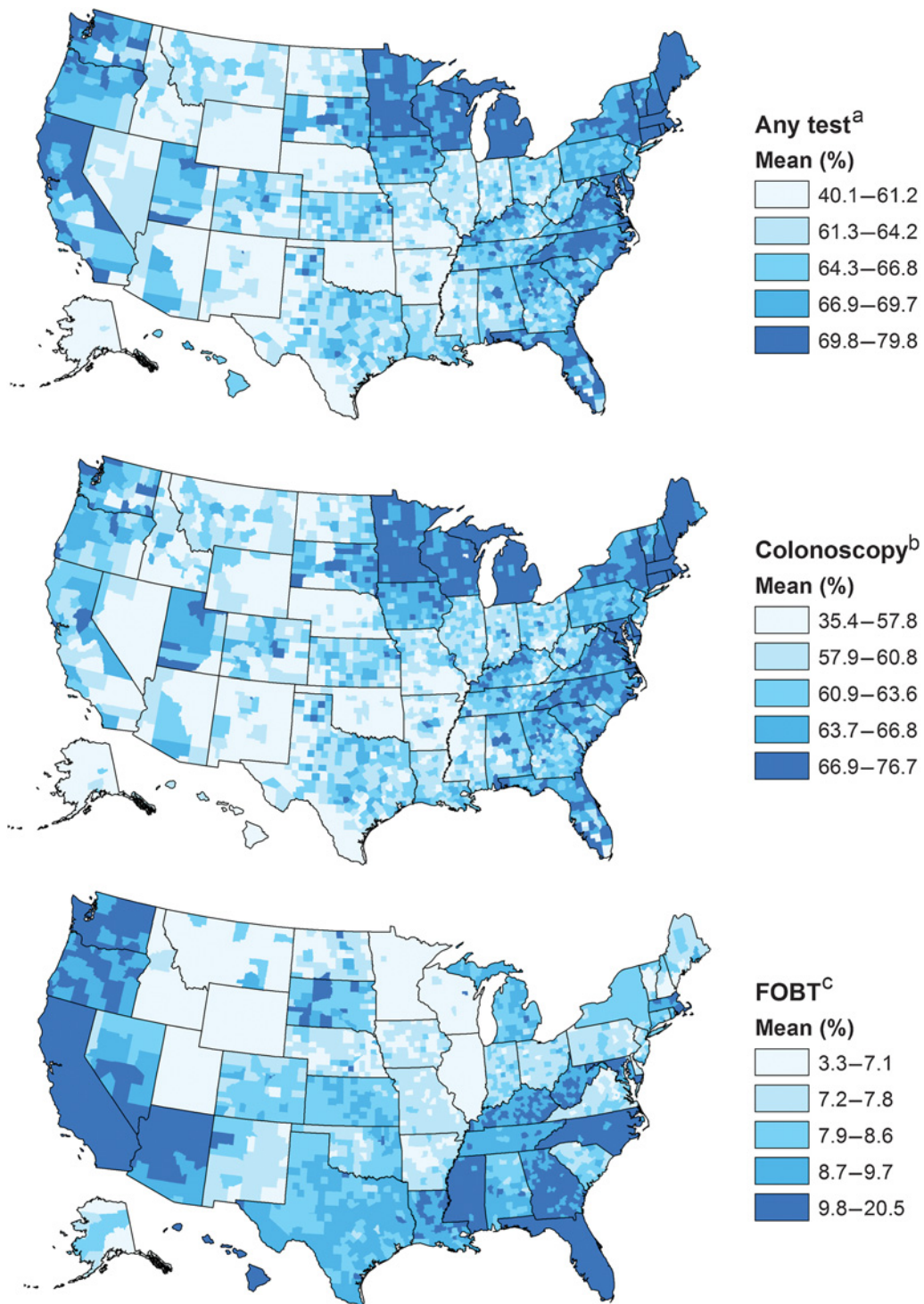


Figure 1. Model-based county estimated prevalence (%) maps for being current with three colorectal cancer test types. The maps show estimated prevalence for (A) any colorectal cancer test type, (B) colonoscopy within 10 years, and (C) FOBT within the past year. Any colorectal cancer test type (A) includes FOBT within the past year; sigmoidoscopy within 5 years with FOBT within 3 years; or colonoscopy within 10 years. The County prevalence shown on the right of each map describes the prevalence by quintiles, each associated with a different color scale.

Despite colorectal cancer screening recommendations published in 2008 and 2016 by the USPSTF emphasizing that no one strategy is advantageous over the other (19, 24), a survey of primary care providers found that most recommended colonoscopy to their patients (25), consistent with our findings. The 2016 recommendations extended the choices in screening tests to align more closely with a patient's preferences, with the goal to maximize the total number of people screened (24). The Community Preventive Services Task Force encourages providers to use reminder systems, small media, such as brochures, videos, or newsletters, to increase awareness about the different tests available, and engage their patients in decision making about a strategy of their choice and availability of services to increase completion rates and follow-up over time (26).

Using small area estimates analysis can potentially highlight barriers to colorectal cancer screening due to geographic accessibility such as travel time and distance to health care facilities, and identify specific geographic locations with these barriers. Several investigators have highlighted the importance of distance to colorectal cancer screening facilities as a barrier to health care (27, 28). Lack of access to health care in rural areas has been well documented and these areas may have higher rates of poverty along with fewer physicians (29). These studies suggest that increasing access to transportation services for populations such as American Indians, or other rural populations living in areas with little or no access to health care facilities, may be an approach to help increase colorectal cancer screening.

Disparities in colorectal cancer screening can result from language or cultural barriers. A national study comparing Latinos and non-Latino whites revealed that Latinos were less likely to have received colorectal cancer screening than were non-Latino whites. Moreover, Latinos responding in Spanish had lower odds of receiving colorectal cancer screening than Latinos responding in English (30, 31). A prospective study from six U.S. states and 2 metropolitan areas found associations between self-reported education and colorectal cancer incidence at the Census tract level (17). This study also observed higher prevalence of adverse health behaviors, such as poor diet, smoking, physical inactivity and unhealthy weight in this population. It is possible that other barriers to screening, such as widespread beliefs and lack of knowledge among county population may contribute to low screening. A literature review of cancer screening interventions in nonclinical community settings was used to derive lessons-learned about effective interventions including cost-sharing elimination for colorectal cancer screening, person-to-person outreach, one-on-one or small groups' education, and mass media interventions (32).

To increase the availability of data about chronic disease in small geographical areas, the CDC Foundation, in collaboration with the Robert Wood Johnson Foundation, launched in 2015 the 500 Cities Project. The project identifies and analyzes city and Census tract-level data using small-area estimation methods for 27 chronic disease measures, five unhealthy behaviors, and nine prevention practices including colorectal cancer testing. The information characterizes the health conditions of these areas' population and helps public health practitioners develop effective and targeted public health interventions for vulnerable populations.

The potential to increase screening rates exists if health-care providers consistently offer multiple screening options and help patients identify the tests they are willing to complete (24). Kaiser has reported being able to achieve screening rates close to or above 80% with an organized approach to screening, starting with FOBT (33, 34). Additionally, states with no high-quality county estimates can use our multilevel small area estimation method to do their own county-level analysis by only including county random effects but no state random effect. All counties in the state can be represented after post-stratification with the Census population data, including counties in BRFSS with no direct estimates. County estimates can help with decisions about resource allocation for interventions on the local level.

Limitations and strengths

Our study has some limitations. First, the results of our study are based on self-reported information, which might be subject to bias. Second, our predicted percentages of being current with colorectal cancer screening might be more appropriate for program planning than for program evaluation. Our model-based estimates might have over-estimated sparsely-populated areas and under-estimated densely-populated areas. Third, we were not able to assess the model's external validity because no other comparable national survey, such as the National Health Interview Survey, had information on colorectal cancer screening in 2014.

Using the large BRFSS data set in multilevel small area estimation models with post-stratification that included geographic and demographic characteristics, and county-level poverty data, is a strength of our study. Our method allows integration with other data sources at the county level, such as Census county data and the American Community Survey, and provides estimates for all the counties. Lastly, our analysis generated consistent estimates when aggregated to the levels of reliable direct BRFSS estimates.

Conclusions

Our analysis highlights the value of having nationwide large surveys, such as BRFSS with linkage to Census county data, to provide information that can be used at the local and state levels and identify patterns of adherence to screening recommendations. We found that state-level information about colorectal cancer screening masks substantial within-state variability. Our study shows that most states and counties in the United States are still far from the "80% by 2018" goal. Our estimates may provide opportunities for municipal, state and federal public agencies to better identify areas in need of coordinated and targeted health promotion efforts, including areas with limited direct BRFSS estimates.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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 or the Economic Research Service, U.S. Department of Agriculture.

Authors' Contributions

Conception and design: Z. Berkowitz, X. Zhang
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Z. Berkowitz, X. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z. Berkowitz, X. Zhang, M. Nadel, J. Holt
Writing, review, and/or revision of the manuscript: Z. Berkowitz, X. Zhang, T.B. Richards, M. Nadel, L.A. Peipins, J. Holt
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Berkowitz, X. Zhang
Study supervision: Z. Berkowitz, X. Zhang

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References

1. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2014 Incidence and Mortality Web-based Report. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2017.
2. Jemal A, Siegel R, Desantis C, Sauer AG. Inequalities in premature death from colorectal cancer by state. *J Clin Oncol* 2015;33:829–35.
3. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst* 2011;103:117–28.
4. Centers for Disease Control and Prevention. Vital signs: colorectal cancer screening test use—United States, 2012. *MMWR Morb Mortal Wkly Rep* 2013;62:881–8.
5. Simon S. Organizations commit to goal of 80% colon cancer testing rate by 2018. Available from: <http://www.cancer.org/cancer/news/organizations-commit-to-goal-of-80-percent-coloncancer-testing-rate-by-2018>.
6. Organizations working together to advance colorectal cancer control efforts. National Colorectal Cancer Roundtable. Available from: <http://ncct.org/tools/80-percent-by-2018>.
7. American Cancer Society. Colorectal cancer facts and figures 2014–2016. Atlanta, GA: American Cancer Society, 2014.
8. Steele BC, Rim SH, Joseph DA, King JB, Seeff LC. Colorectal cancer incidence and screening—United states, 2008 and 2010. *MMWR Morb Mortal Wkly Rep* 2013;62:53–60.
9. Shapiro JA, Klabunde CN, Thompson TD, Nadel MR, Seeff LC. Patterns of colorectal cancer test use, including CT colonography, in the 2010 national Health Interview Survey. *Cancer Epidemiol Biomarkers Prev* 2012;21:895–904.
10. Office of Surveillance, Epidemiology and Laboratory Services. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System: 2014 Summary Data Quality Report. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
11. Colditz GA, McGowan LD, James AS, Bohike K, Goodman AS. Screening for colorectal cancer: using data to set prevention priorities. *Cancer Causes Control* 2014;25:93–8.
12. Zhang X, Holt JB, Lu H, Wheaton AG, Ford ES, Greenlund KJ, et al. Multilevel regression and post stratification for small-area estimation population health outcomes: a case study of chronic obstructive pulmonary disease prevalence using the Behavioral Risk Factor Surveillance System. *Am J Epidemiol* 2014;179:1025–33.
13. Zhang Xingyou, Holt JB, Yun S, Lu H, Greenlund KJ, Croft JB. Validation of multilevel regression and poststratification methodology for small area estimation of health indicators from the Behavioral Risk Factor Surveillance System. *Am J Epidemiol* 2015;182:127–37.
14. United States Census Bureau. Population Division. Annual Estimates of the Resident Population by Sex, Race, and Hispanic Origin for the United States, States, and Counties. Available from: <https://www.census.gov/data/datasets/2016/demo/popest/counties-detail.html>.
15. Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, Bridged Race Categories. Vintage 2014 Bridged-Race Postcensal Population Estimates. Available from: http://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm.
16. Boscoe FP, Henry KA, Sherman RL, Johnson CJ. The relationship between cancer incidence, stage and poverty in the United States. *Int J Cancer* 2016;139:607–12.
17. Doubeni CA, Major JM, Laiyemo AO, Schootman M, Zuber AG, Hollenbeck AR, et al. Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. *JNCI J Natl Cancer Inst* 2012;104:1353–62.
18. United States Census Bureau. American Community survey 2010 – 2014 state level estimation details.
19. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627–37.
20. Louise R. Spatial epidemiology: some pitfalls and opportunities. *Epidemiology* 2009;20:242–4.
21. Condon P. Mixture of spatial and unstructured effects for spatially discontinuous health outcomes. *Computational Stat Data Anal* 2007; 51:3197–212.
22. Norris T, Vines PL, Hoeffel EM. The American Indian and Alaska Native Population: 2010. 2010 Census briefs. United States Census Bureau, 2012. [Accessed date: 01/04/2018]. Available from: <http://www.census.gov/prod/cen2010/briefs/c2010br-10.pdf>.
23. Norris T, Vines PL, Hoeffel EM. The Hispanic Population: 2010. 2010 Census briefs. United States Census Bureau, 2011. Available from: <http://www.census.gov/prod/cen2010/briefs/c2010br-04.pdf>.
24. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *JAMA* 2016; 315:2564–75.
25. Zapka J, Klabunde CN, Taplin S, Yuan G, Ransohoff D, Kobrin S. Screening colonoscopy in the US: attitudes and practices of primary care physicians. *J Gen Intern Med* 2012;27:1150–8.
26. The Community Guide. Cancer screening: multicomponent interventions—colorectal cancer. 2016. Available from: <http://www.thecommunityguide.org/cancer>.
27. Wheeler SB, Kuo T, Goyal RK, Myer A, Lich K, Gillen EM, et al. Regional variation in colorectal cancer testing and geographic availability in a publicly insured population. *Health Place* 2014;29:114–23.
28. Sherman RL, Henry KA, Tannenbaum SL, Feaster DJ, Kobetz E, Lee DJ. Applying spatial analysis tools in public health: an example using SaTScan to detect geographic targets for colorectal cancer screening interventions. *Prev Chronic Dis* 2014;11:E41.
29. Caldwell JT, Ford CL, Wallace SP, Wang MC, Takahashi LM. Intersection of living in rural versus urban area and race/ethnicity in explaining access to health care in the United States. *Am J Public Health* 2016;106:1463–9.
30. Diaz JA, Roberts MB, Goldman RE, Weitzen S, Eaton CB. Effect of language on colorectal cancer screening among Latinos and non-Latinos. *Cancer Epidemiol Biomarkers Prev* 2008;17:2169–73.
31. Diaz JA, Roberts MB, Clarke JG, Simmons EM, Goldman RE, Rakowski W. Colorectal cancer screening: language is a greater barrier for latino men than latino women. *J Immigrant Minority Health* 2013;15:472–5.
32. Pasick RJ, Hiatt RA, Paskett ED. Lessons learned from community-based cancer screening intervention research. *Cancer* 2004;101:1146–64.
33. Levin TR, Jamieson L, Burley DA, Reyes J, Oehrli M, Caldwell C. Organized colorectal cancer screening in integrated health care systems. *Epidemiol Rev* 2011;33:101–10.
34. Lee JK, Levin TR, Corley DA. The road ahead: what if gastroenterologists were accountable for preventing colorectal cancer? *Clin Gastroenterol Hepatol* 2013;11:204–7.

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