

Early-Onset Colorectal Cancer Mortality Trends across the U.S. Rural-Urban Continuum, 1999-2020: A Population-Based Ecological Study

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How to cite this paper: Brady, H.W., Gill, J., Roberts, M. and Mbachi, C. (2026) Early-Onset Colorectal Cancer Mortality Trends across the U.S. Rural-Urban Continuum, 1999-2020: A Population-Based Ecological Study. *Health*, **18**, 649-661.
<https://doi.org/10.4236/health.2026.187039>

Received: May 26, 2026

Accepted: July 5, 2026

Published: July 8, 2026

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Abstract

Background/Objectives: Early-onset colorectal cancer (EOCRC) mortality has increased among younger adults in the United States, while rural-urban disparities in colorectal cancer outcomes remain persistent. This study evaluated EOCRC mortality trends among adults aged 25 - 44 years from 1999 to 2020 across the U.S. rural-urban continuum. **Methods:** We conducted a retrospective, population-based ecological study using the CDC WONDER Underlying Cause of Death database. Deaths were identified using ICD-10 codes C18-C20 for colorectal cancer as the underlying cause of death. Age-adjusted mortality rates (AAMRs) per 100,000 population were standardized to the 2000 U.S. standard population and stratified by 2013 National Center for Health Statistics urban-rural classification categories. Temporal trends were assessed using joinpoint regression to estimate annual percent change and average annual percent change (AAPC). **Results:** From 1999 to 2020, 37,459 EOCRC deaths occurred among U.S. adults aged 25 - 44 years. National AAMRs increased from 2.0 to 2.4 per 100,000, corresponding to an AAPC of +0.79% per year (95% CI: 0.63 - 0.95; $p < 0.0001$). Mortality increased across all urbanization categories, with predominantly linear trends. Nonmetropolitan counties had the highest absolute mortality rates, reaching 3.1 per 100,000 in both micropolitan and noncore areas by 2020. AAPCs ranged from +0.70% to +1.15% across urbanization categories, with no statistically significant pairwise differences. **Conclusions:** EOCRC mortality increased steadily across the U.S. rural-urban continuum, with persistently higher absolute mortality in nonmetropolitan populations. These findings support geographically targeted

strategies to improve early detection, screening access, and colorectal cancer outcomes among younger adults.

Keywords

Early-Onset Colorectal Cancer, Colorectal Cancer Mortality, Rural-Urban Disparities, Age-Adjusted Mortality Rate, CDC WONDER, Joinpoint Regression, Cancer Epidemiology, Geographic Disparities, Nonmetropolitan Health, Population-Based Study

1. Introduction

Early-onset colorectal cancer (EOCRC), defined as individuals < 50 years old diagnosed with colorectal cancer (CRC), has emerged as a rising concern in the United States (US) [1]. While overall CRC mortality has decreased among older adults, EOCRC mortality has increased. Concerningly, EOCRC is now among the leading causes of cancer-related death in adults aged 20 - 49 years [2]. These trends suggest shifting epidemiologic dynamics, including generational risk exposures, delayed diagnosis, and potential gaps in preventive strategies targeting younger adults.

Geographical context is critical when evaluating cancer mortality trends. Prior research has demonstrated that mortality from all cancers is higher in nonmetropolitan than in large metropolitan areas in the US [3]. Geographic variation reflects population demographic characteristics and differences in the prevalence of cancer risk factors, detection practices, and access to care. CRC mortality has consistently been associated with higher rates in rural areas compared to urban populations [4]. This disparity has been associated with low socioeconomic status, household characteristics, and racial/ethnic minority status in rural areas, in addition to known differences in risk-factor prevalence such as smoking, obesity, and physical inactivity [4] [5]. Importantly, temporal data suggest that these rural-urban gaps are not narrowing, underscoring the need for continued longitudinal surveillance [6].

Mortality surveillance stratified by level of urbanization is therefore essential to determine whether EOCRC trends are evolving uniformly or disproportionately affecting specific community types. National averages may obscure meaningful heterogeneity across the rural-urban continuum [7] [8]. Examining trends across the Urban-Rural Classification Scheme allows for a more granular assessment of whether mortality risk follows a stepwise gradient rather than a simple rural-urban dichotomy. Such stratification enables identification of communities experiencing the steepest increases in EOCRC mortality and provides critical evidence to guide geographically targeted prevention strategies, diagnostic access initiatives, and resource allocation.

Accordingly, this study utilizes the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) to ex-

amine EOCRC across the rural-urban continuum. By analyzing age-adjusted mortality rates stratified by standardized National Center for Health Statistics urbanization categories, this approach enables a granular evaluation of temporal patterns across large metropolitan, fringe, medium, small metro, micropolitan, and noncore counties, providing nationally representative insight into emerging geographic disparities among younger adults with CRC. The objective of this study was to evaluate temporal trends in EOCRC mortality across the U.S. rural-urban continuum from 1999-2020 and assess whether mortality trajectories differ by level of urbanization and race.

2. Methods

This was a retrospective, population-based study using the CDC WONDER Underlying Cause of Death database. Age-adjusted mortality rates (AAMRs), annual death counts, population estimates, and crude mortality rates for individuals aged 25 - 44 years were extracted for 1999-2020 [9] [10]. AAMRs per 100,000 person-years were standardized to the 2000 U.S. standard million population via the direct method.

Deaths were identified using the underlying cause of death filter with International Classification of Diseases, Tenth Revision (ICD-10) codes C18-C20 (malignant neoplasms of the colon, rectosigmoid junction, and rectum) and year of death. Inclusion criteria were U.S. residents aged 25 - 44 years with CRC (ICD-10 C18-C20) listed as the underlying cause of death. Analyses were restricted to individuals aged 25 - 44 years because CDC WONDER provides age-adjusted rates using standard 10-year age groups. Because fully cross-classified race-by-urbanization-by-year strata frequently fell below the CDC WONDER reporting threshold (counts below 10 or rates flagged as unreliable), suppressed cells were not extracted; race-stratified analyses were instead conducted using collapsed metropolitan and nonmetropolitan groupings. Within these groupings, non-Hispanic White and non-Hispanic Black populations yielded annual death counts that met CDC WONDER reporting criteria across the full study period (1999-2020), so no observations required exclusion from the reported race-stratified models. Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander populations remained below the reporting threshold even after collapsing and therefore could not be analyzed.

Urbanization categories were defined using the 2013 National Center for Health Statistics (NCHS) urban-rural classification scheme [11]. This scheme categorizes US counties into six mutually exclusive levels: 1) Large Central Metropolitan (urban core counties in areas ≥ 1 million population), 2) Large Fringe Metropolitan (suburban counties in areas ≥ 1 million), 3) Medium Metropolitan (250,000 - 999,999), 4) Small Metropolitan ($<250,000$), 5) Micropolitan (urban clusters 10,000 - 49,999, nonmetropolitan), and 6) NonCore (rural, nonmetropolitan) [11]. Primary analyses evaluated trends across all six urbanization categories. Race and ethnicity were defined using the CDC WONDER bridged-race and His-

panic-origin variables. Decedents were classified into bridged-race categories (White; Black or African American; American Indian or Alaska Native; Asian or Pacific Islander) in combination with Hispanic origin (Hispanic or Latino; Not Hispanic or Latino). Race-stratified analyses were restricted to non-Hispanic White and non-Hispanic Black individuals; Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander populations were not analyzed separately because annual stratum-specific death counts frequently fell below 10 or produced rates flagged as unreliable by CDC WONDER, precluding stable trend estimation. For race-stratified analyses, categories were collapsed into metropolitan (Large Central, Large Fringe, and Medium Metropolitan) and nonmetropolitan (Small Metropolitan, Micropolitan, and NonCore) groups to improve rate stability and minimize suppression from small cell counts (<10 deaths or unreliable rates per CDC guidelines).

Mortality from EOCRC was represented using AAMRs per 100,000 population obtained directly from CDC WONDER. Study size was determined by the total number of eligible EOCRC deaths recorded during the study period. No individual-level covariates were available for analysis.

Annual Percent Change (APC) quantifies the average yearly rate of change over specific segments in the joinpoint model. Average Annual Percent Change (AAPC) is the weighted average of APCs over the entire 1999-2020 period. Trends were significantly increasing/decreasing if APC/AAPC differed from zero ($p < 0.05$); otherwise stable (95% CI including zero).

Temporal trends in EOCRC mortality were evaluated using joinpoint regression in the Joinpoint Regression Program (Version 5.4.0; Surveillance Research Program, US National Cancer Institute) and parallel verification in R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) via the segmented package. AAMR served as the dependent variable and calendar year as the independent variable. Standard errors were derived from reported 95% confidence intervals by assuming approximate normality and dividing the confidence interval width by 2×1.96 .

In Joinpoint, the Grid Search method identified joinpoints, requiring a minimum of two observations before/after the first/last joinpoint and between segments. No grid points were placed between observed x-values (default), and no minimum percentage point difference was enforced between segments. Models allowed 0 - 4 joinpoints, with selection via Weighted Bayesian Information Criterion (WBIC). Significance used Monte Carlo permutation (5001 resamples). Confidence intervals for annual percent change (APC) and average annual percent change (AAPC) employed the Empirical Quantile method. Log-linear Joinpoint regression models were used to estimate temporal trends in rates. Segment-specific APCs were derived from the slope of each model as $100 \times (e^{\beta_1} - 1)$, and AAPC for 1999-2020 was calculated as the weighted average of segment-specific APCs across the study interval.

In R, log-transformed ASMRs were modeled against year. A linear model (0

joinpoints) was baseline; segmented models allowed 1 - 2 joinpoints with proportionally spaced initial breakpoints. Selection used the lowest Akaike Information Criterion (AIC). Unstable segmented estimates defaulted to linear. APC derived as 100× slope from the log-linear model. Pairwise APC comparisons between subgroups used z-tests, with statistical significance defined as $p < 0.05$. Because multiple pairwise comparisons were performed without correction, these comparisons were treated as exploratory and hypothesis-generating rather than confirmatory; no adjustment for multiple testing was applied, and the resulting p-values should be interpreted accordingly. The NCI Joinpoint Regression Program served as the primary analytic platform, and all APC and AAPC values reported in the Results were generated in Joinpoint; the R segmented analysis was used solely as a confirmatory cross-check. When the two platforms disagreed, or when segmented models in either program produced unstable or non-estimable segment-specific estimates, the more parsimonious linear (0-joinpoint) model was retained as the final reported model.

3. Results

3.1. National Trends in EOCRC

From 1999 to 2020, a total of 37,459 EOCRC deaths occurred across all U.S. counties. A full breakdown of mortality counts by region is available in [Table 1](#). National AAMRs showed a steady upward trend, increasing from 2.0 per 100,000 in 1999 to 2.4 per 100,000 in 2020 ([Figure 1](#)). The mean AAMR across the period was 2.28 per 100,000.

Table 1. Descriptive characteristics of early-onset colorectal cancer mortality by urbanization category, united states, 1999-2020.

Urbanization Category	Total Deaths	Population Range
Large Central Metropolitan	11,516	27,332,917 - 30,448,319
Large Fringe Metropolitan	8845	20,183,888 - 21,621,975
Medium Metropolitan	7581	16,463,207 - 17,903,696
Small Metropolitan	3296	7,032,592 - 7,460,303
Micropolitan	3540	6,429,076 - 7,194,826
Noncore	2681	4,212,601 - 5,043,622

Joinpoint regression (NCI Joinpoint Program) and parallel segmented regression in R consistently identified linear trends (0 joinpoints) as the best-fitting model across nearly all primary and stratified analyses, indicating no statistically significant changes in slope over the period. In cases of linear models (no joinpoints detected), the average annual percent change (AAPC) over the full 1999-2020 interval was identical to the overall APC. The national AAPC was +0.79% per year (95% CI: 0.63 - 0.95; $p < 0.0001$).

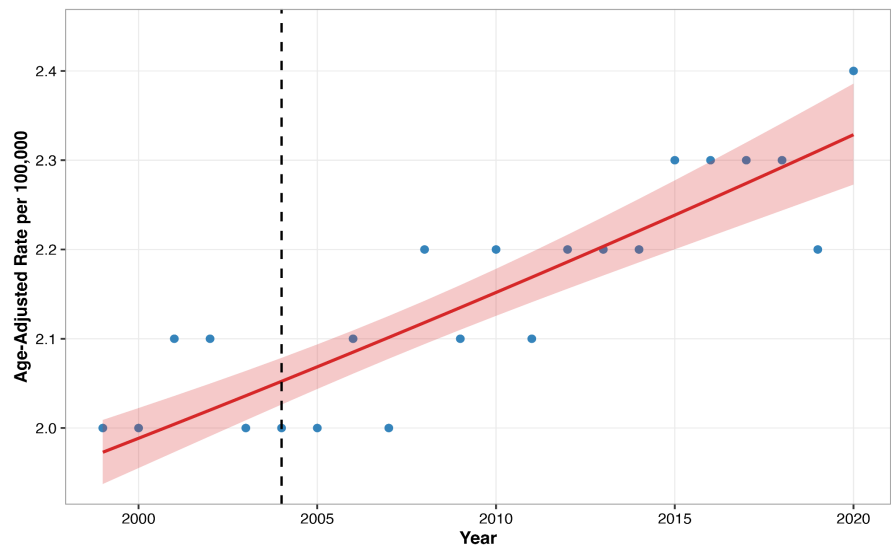


Figure 1. National age-adjusted mortality rates for early-onset colorectal cancer, United States, 1999-2020. Observed rates (blue points), fitted trend (red line), and joinpoint detection (dashed line) from joinpoint regression with 95% confidence band (shaded).

3.2. Trends in Urbanization and Rural Areas

AAMRs for EOCRC exhibited upward trends across all urbanization categories from 1999 to 2020, with linear patterns predominant in final models.

In large central metropolitan counties, rates increased steadily from 1.8 per 100,000 in 1999 to 2.3 in 2020 (AAPC +0.77%; 95% CI: 0.35 - 1.19; $p = 0.002$). Large fringe metropolitan areas showed a similar overall rise from 1.8 to 2.3 (AAPC +0.99%; 95% CI: 0.66 - 1.33; $p < 0.0001$); although joinpoint regression initially suggested a segmented model (inflection points near 2001 and 2003), segment-specific APCs were not reliably estimable, and the linear summary held.

Medium metropolitan counties experienced a gradual increase from 1.9 to 2.2 (AAPC +0.70%; 95% CI: 0.34 - 1.05; $p = 0.001$), with any detected change points (around 2012 and 2014) not yielding stable segments. Small metropolitan areas followed a purely linear increase from 2.1 to 2.4 (AAPC +1.02%; 95% CI: 0.55 - 1.49; $p < 0.001$). Urban temporal trends are demonstrated in **Figure 2**.

Rural counties consistently displayed higher baseline mortality rates and numerically larger increases. In micropolitan (nonmetropolitan) counties, AAMRs rose linearly from 2.3 in 1999 to 3.1 in 2020 (AAPC +1.15%; 95% CI: 0.58 - 1.72; $p = 0.001$). Noncore (nonmetropolitan) counties began at 2.6 in 1999 and reached 3.1 in 2020 (AAPC +0.97%; 95% CI: 0.46 - 1.48; $p = 0.001$), showing the highest absolute rates. Rural temporal trends are demonstrated in **Figure 3**.

Table 2 summarizes the age-adjusted mortality rates and trends across all urbanization categories.

No pairwise differences in AAPCs between urbanization categories reached statistical significance (all $p \geq 0.189$), suggesting that while rural categories showed numerically higher AAPCs and absolute mortality rates, the rate of increase did not differ significantly from urban categories after accounting for variability.

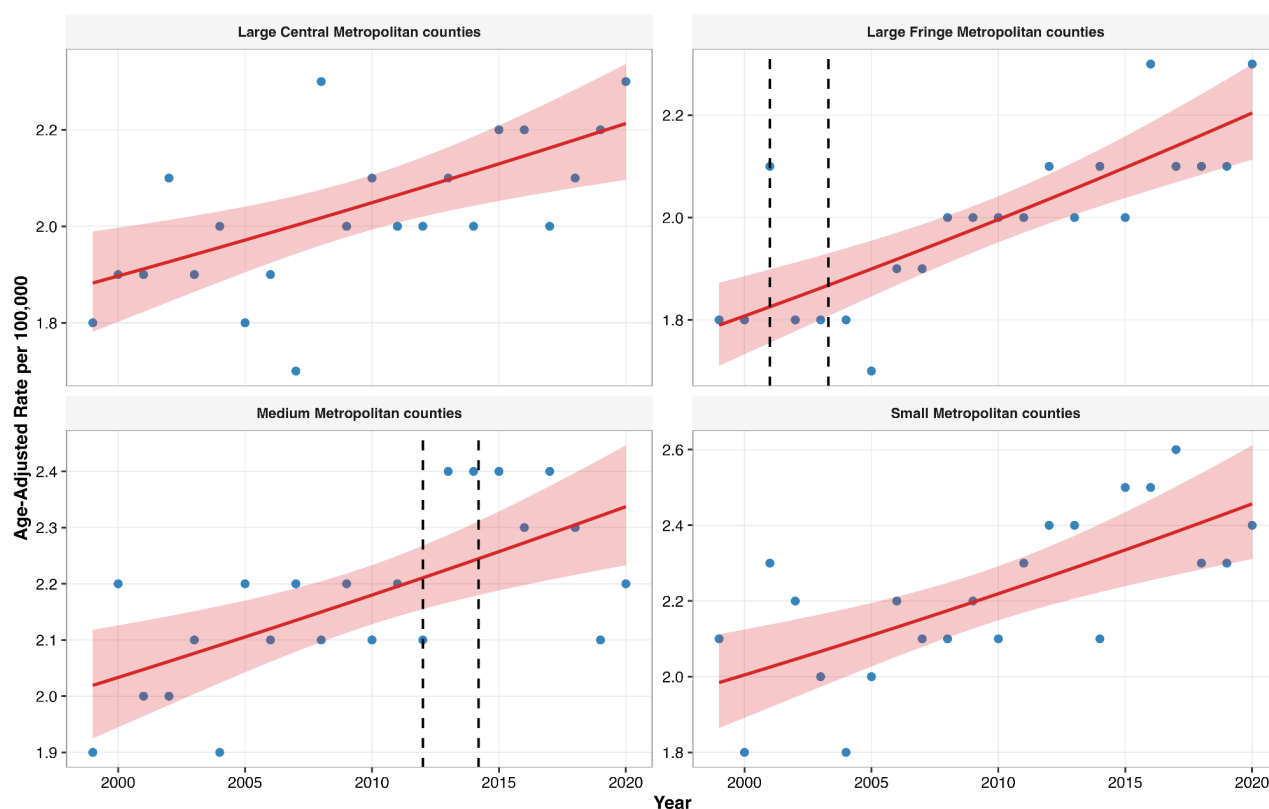


Figure 2. Urban age-adjusted mortality rates for early-onset colorectal cancer, United States, 1999–2020. Observed rates (blue points), fitted trend (red line), and joinpoint detection (dashed line) from joinpoint regression with 95% confidence band (shaded).

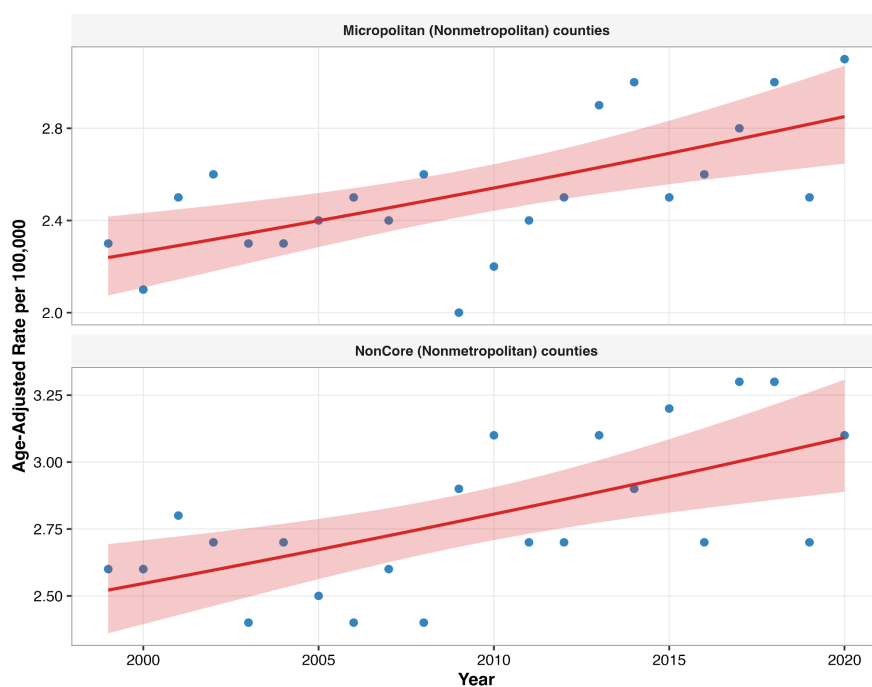


Figure 3. Rural age-adjusted mortality rates for early-onset colorectal cancer, United States, 1999–2020. Observed rates (blue points), fitted trend (red line), and joinpoint detection (dashed line) from joinpoint regression with 95% confidence band (shaded).

Table 2. Age-adjusted mortality rates (AAMR) and joinpoint regression trends for early-onset colorectal cancer mortality (ages 25 - 44 years) by NCHS urbanization category, United States, 1999-2020.

Urbanization category	AAMR, 1999 → 2020 (% change)	AAPC, % (95% CI); p-value
Large central metropolitan	1.8 → 2.3 (+27.8%)	0.77 (0.35 - 1.19); p = 0.0019
Large fringe metropolitan	1.8 → 2.3 (+27.8%)	0.99 (0.66 - 1.33); p < 0.001
Medium metropolitan	1.9 → 2.2 (+15.8%)	0.70 (0.34 - 1.05); p = 0.0011
Small metropolitan	2.1 → 2.4 (+14.3%)	1.02 (0.55 - 1.49); p < 0.001
Micropolitan	2.3 → 3.1 (+34.8%)	1.15 (0.58 - 1.72); p < 0.001
Noncore	2.6 → 3.1 (+19.2%)	0.97 (0.46 - 1.48); p = 0.0013
National	2.0 → 2.4 (+20.0%)	0.79 (0.63 - 0.95); p < 0.0001

AAMR = age-adjusted mortality rate; AAPC = average annual percent change; CI = confidence interval. AAMRs are reported per 100,000 population. AAPCs were estimated using log-linear Joinpoint regression models.

3.3. Trends by Race and Geographic Classification

When stratified by race and geographic classification, divergent mortality trends emerged between Black and White populations, with linear models predominant.

Among Black individuals in metropolitan counties, EOCRC mortality rates remained relatively stable (AAPC -0.21%; 95% CI: -0.63 to 0.22; p = 0.34). In non-metropolitan counties, Black individuals experienced a significant decline (AAPC -1.29%; 95% CI: -2.20 to -0.37; p = 0.006).

Among White individuals, mortality increased significantly in both settings. Metropolitan White populations showed a linear AAPC of +1.19% per year (95% CI: 0.94 - 1.43; p < 0.001); although joinpoint suggested inflections around 2007-2008 in some runs, segments were not reliably estimable. Nonmetropolitan White individuals had a comparable linear AAPC of +1.19% (95% CI: 0.70 - 1.67; p < 0.001). Age-adjusted mortality rates by metropolitan/nonmetropolitan and race are provided in **Figure 4**.

Pairwise comparisons of AAPC estimates demonstrated significant differences in mortality trends between several race-geography groups. Mortality trends among Black individuals differed significantly between metropolitan and non-metropolitan counties (p = 0.037). The increasing trends among White populations were significantly greater than those among Black populations in both metropolitan (p < 0.001) and nonmetropolitan settings (p < 0.001). No statistically significant difference was observed between White metropolitan and White non-metropolitan trends (p = 1.00), indicating similar upward trajectories across geographic contexts within the White population.

4. Discussion

This population-based analysis of CDC WONDER data from 1999 to 2020 revealed a persistent and linear increase in EOCRC mortality among U.S. adults

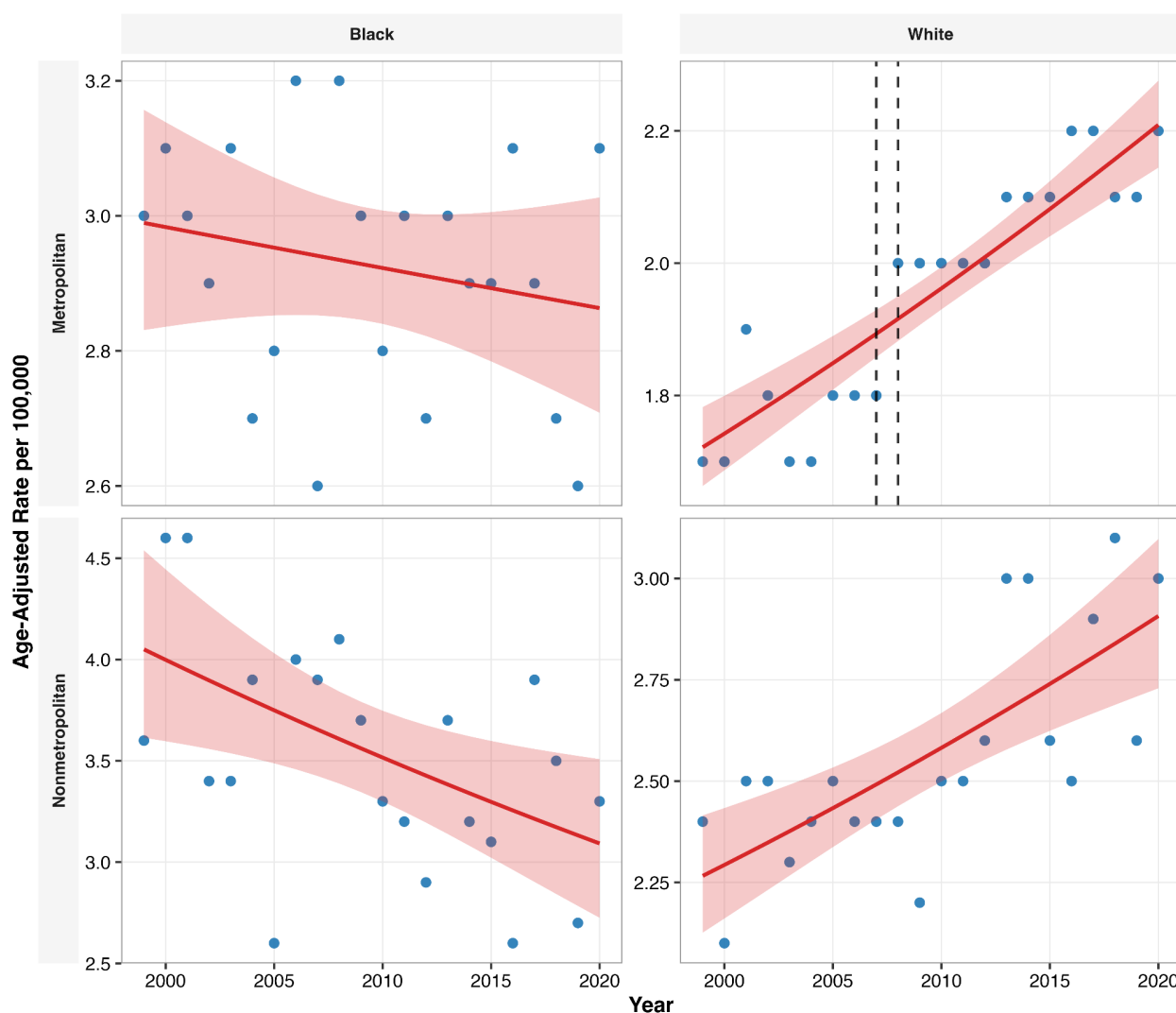


Figure 4. Age-adjusted mortality rates for early-onset colorectal cancer by race and metropolitan versus nonmetropolitan, United States, 1999–2020. Observed rates (blue points) and fitted trend (red line) from joinpoint regression with 95% confidence band (shaded).

aged 25–44 years, with age-adjusted mortality rates (AAMRs) rising nationally from 2.0 to 2.4 per 100,000 (AAPC +0.79%). The consistent linear trends indicate gradual worsening over time rather than abrupt epidemiologic shifts. While prior studies have documented increasing EOCRC incidence and mortality nationally, this study provides novel evidence that these mortality increases persist across the full rural-urban continuum, with nonmetropolitan populations experiencing the highest absolute mortality burden throughout the study period. These findings suggest that national aggregate trends may obscure important and persistent geographic inequities in EOCRC mortality.

Nonmetropolitan counties exhibited the highest absolute AAMRs (up to 3.1 per 100,000 by 2020) and steeper AAPCs (+1.15% in micropolitan, +0.97% in noncore) compared to metropolitan categories (AAPCs +0.70%–1.02%). Although pairwise comparisons showed no statistically significant differences in AAPCs across

urbanization levels (all $p \geq 0.189$), the consistent stepwise pattern, higher baseline rates, and greater relative growth in rural areas suggest a widening geographic disparity over time. These findings align with prior evidence of elevated CRC outcomes in rural populations [4] [12] [13], as well as the broader birth cohort effect driving rising EOCRC risk across successive generations. Rural excesses in EOCRC have been documented, with rural incidence increases outpacing urban ones in some analyses (e.g., 35% vs. 20% rise from 2000-2016) [14]. Our mortality-focused findings extend this pattern, highlighting that rural communities bear a disproportionate and growing share of the EOCRC burden despite lower absolute death counts in large central metropolitan areas.

Racial stratification revealed stark divergences. Among White populations, significant linear increases occurred in both metropolitan and nonmetropolitan settings (AAPC +1.19% in each), with no geographic difference ($p = 1.00$). In contrast, Black populations showed stability or significant decline (metropolitan AAPC -0.21%, nonmetropolitan -1.29%; $p = 0.037$ for metropolitan vs. nonmetropolitan difference), resulting in markedly lower trends than Whites (both $p < 0.001$). These patterns contrast with overall CRC trends, where Black populations often experience higher burdens, but align with emerging reports of stabilizing or declining EOCRC mortality in Black groups amid rising rates in Whites and other minorities [15] [16]. Potential explanations include differential risk factor exposures, screening uptake, or diagnostic delays, though our data cannot directly adjudicate these [14].

Several mechanisms may underlie the observed trends and disparities. The linear, cohort-like increases across all strata point to generational shifts in modifiable risk factors, including obesity, Western dietary patterns (high red/processed meat, low fiber), physical inactivity, alcohol use, and microbiome alterations from antibiotics or diet [1] [17]. These exposures are more prevalent in rural areas, where obesity, smoking, and sedentary behavior exceed urban levels, may be associated with EOCRC risk [18]-[20]. Rural-urban gaps in healthcare access, longer travel distances, fewer specialists, lower insurance coverage, and reduced primary care availability, are consistent with delayed diagnosis and suboptimal treatment, exacerbating mortality despite similar or lower incidence in some rural settings [21]-[23]. Lower CRC screening uptake in rural populations further compounds risks, as early detection remains limited for those under 50 (current guidelines start at 45) [24] [25]. Socioeconomic factors, including poverty and education disparities concentrated in rural and certain racial groups, may interact with these barriers.

The absence of joinpoints in all models suggests no major period-specific interventions (e.g., screening guideline changes) substantially altered trajectories during the study period, reinforcing the need for proactive strategies. While absolute deaths were highest in large central metropolitan counties (reflecting population density), the relative growth in rural areas signals emerging inequities that could widen further without intervention.

Strengths of this study include its use of nationally representative mortality data

from CDC WONDER, enabling comprehensive population-level analysis across the United States. The application of granular NCHS urbanization categories allowed for detailed assessment across the full rural-urban continuum rather than a simplified dichotomous classification. Additionally, temporal trends were evaluated using both the NCI Joinpoint Regression Program and parallel modeling in R, enhancing the robustness and reproducibility of findings. The focus on mortality provides complementary insight to prior incidence-based studies, offering a more complete understanding of EOCRC burden.

Despite these strengths, several limitations warrant consideration. The ecological design precludes individual-level inference and limits the ability to adjust for potential confounders such as socioeconomic status, comorbidities, and access to care. Mortality data derived from death certificates may be subject to misclassification of the underlying cause of death. Suppression of small cell counts in CDC WONDER necessitated aggregation of urbanization categories for race-stratified analyses, which may obscure more granular differences. Analyses were restricted to non-Hispanic White and non-Hispanic Black populations due to data suppression in other groups, potentially limiting generalizability. Additionally, the absence of stage at diagnosis and treatment data limits interpretation of underlying drivers of observed mortality trends. Finally, this study defined early-onset colorectal cancer as disease occurring in adults aged 25 - 44 years, the range corresponding to the standard 10-year age groups (25 - 34 and 35 - 44 years) reported by CDC WONDER. This explicitly bounded window was selected to ensure stable, age-standardized, and reproducible estimates; although some studies adopt a broader definition extending to all adults younger than 50 years, the 25 - 44-year definition isolates a clearly specified segment of the early-onset population and should be interpreted as such in cross-study comparisons.

5. Conclusion

These findings underscore widening geographic and racial inequities in EOCRC mortality, with rural populations facing higher absolute risks and comparable or greater relative increases. Targeted public health efforts are urgently needed: expanding access to screening (e.g., lowering age to 45 nationwide with rural outreach), symptom awareness campaigns for younger adults, risk factor modification (obesity prevention, diet/exercise promotion), and equitable oncology care delivery in underserved areas. Future research should incorporate stage-specific data, individual-level risk factors, and interventions to mitigate rural-urban gaps, ultimately reducing the growing EOCRC burden in vulnerable communities.

Acknowledgements

The authors would like to acknowledge the research department at Lincoln Memorial University-DeBusk College of Osteopathic Medicine for their help in the review of this manuscript, specifically, Ms. Amanda McCoy and Dr. Bradley Fleenor.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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