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Original Article

Long-Term Shifts and Disparities in Colorectal Cancer Mortality in the United States: A Population-Based Analysis (1999–2023)

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ABSTRACT

Background: Colorectal cancer (CRC) remains a leading cause of cancer-related mortality in the United States despite advances in screening and treatment. Prior national studies have documented long-term declines in CRC mortality; however, emerging demographic and disparities warrant updated evaluation.
Methods: We conducted a retrospective, population-based analysis of CRC mortality in the United States from 1999 to 2023 using the CDC WONDER database. Adults aged ≥ 25 years with CRC were identified using ICD-10 codes C18–C20. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated. Trends were assessed using Joinpoint regression.
Results: From 1999 to 2023, a total of 1,551,550 CRC deaths were recorded among U.S. adults aged ≥ 25. The overall AAMR declined from 38.23 per 100,000 in 1999 to 22.93 in 2023 (AAPC: −2.14; 95% CI: −2.39 to −1.88; $p < 0.001$). Overall, the AAMR declined in both sexes between 1999 and 2023; 31.98 to 19.09 (AAPC: −2.16; $p < 0.01$) among women, as compared to 47.46 to 27.43 (AAPC: −2.31; $p < 0.01$) among men. Racial disparities persisted, with non-Hispanic Black individuals showing the highest overall AAMR (37.34). Regionally, the Midwest has the highest overall AAMR (30.05). Urban–rural comparisons (1999–2020) showed higher AAMRs in rural areas (32.08) than in metropolitan areas (27.81). Older adults (≥ 65 years) accounted for most deaths. The most common place of death was home (40.7%).
Conclusions: CRC mortality in the U.S. has declined substantially over the past 25 years; however, significant disparities persist by race, geography, and age.

1. Introduction

Colorectal cancer (CRC) is one of the most common yet preventable cancers worldwide. Despite significant advances in screening, early detection, and treatment over the past decades, CRC remains a leading cause of cancer-related mortality in the United States. The disease can develop through multiple pathways, including the adenoma-carcinoma sequence and the serrated pathway. Risk factors range from modifiable lifestyle factors such as diet, obesity, and smoking to non-modifiable factors, including age, genetic predisposition, and inflammatory bowel disease [1, 2].

According to the American Cancer Society, CRC is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the United States. In 2023, an estimated 153,020 new cases of CRC were diagnosed, with approximately 52,550 deaths attributed to the disease [3]. While overall CRC incidence and mortality rates in the U.S. have been declining among older adults (≥50 years) since the widespread implementation of colonoscopy screening programs in the early

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2000s [4, 5], concerning trends have emerged showing rising rates among younger adults under 50 years of age [5, 6].

CRC typically presents with symptoms such as changes in bowel habits, rectal bleeding, abdominal pain, unexplained weight loss, and iron-deficiency anemia. However, many early-stage cancers remain asymptomatic, underscoring the critical importance of screening programs. The United States Preventive Services Task Force (USPSTF) currently recommends CRC screening beginning at age 45 for average-risk individuals, updated from the previous recommendation of age 50 in response to the increasing incidence among younger populations [7]. Screening options include colonoscopy, FIT testing, CT colonography, and stool DNA-based tests, with colonoscopy considered the gold standard because it allows for both the detection and removal of precancerous polyps. When CRC is diagnosed, staging follows the TNM classification system, which informs treatment decisions, ranging from surgical resection for early-stage disease to combined chemotherapy, targeted therapy, and immunotherapy in advanced stages [8].

Treatment outcomes have improved dramatically in the U.S. where the overall 5-year relative survival is approximately 65%, although this varies greatly according to the stage at diagnosis from over 90% for localized disease to about 15% once distant metastases are present [9]. These disparities in survival highlight the crucial role of early detection through screening programs. Despite these advances, significant disparities persist in U.S. CRC outcomes across demographic groups. Studies in the U.S. have demonstrated differences in incidence, mortality, screening rates, and survival based on race, ethnicity, socioeconomic status, and geographic location [10, 11].

Despite the recent reports, gaps remain in understanding recent mortality patterns, particularly among younger adults. This study examined colorectal cancer mortality trends in the U.S. from 1999–2023 among adults aged 25 years and older, using joinpoint regression to analyze trends across age, sex, race/ethnicity, and other risk factors to identify disparities and inform targeted interventions.

2. Methods

2.1. Study Design and Population

This study used a retrospective, population-based design to evaluate long-term trends and disparities in CRC-related mortality in the United States from 1999 to 2023. Mortality data were obtained from the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause-of-Death database. The analysis included all adults aged 25 years and older, a threshold selected to ensure stable estimates and minimize data suppression commonly observed in younger age groups. CRC – related deaths were identified using the International Classification of Diseases, 10th Revision (ICD10), including malignant neoplasms of the colon (C18), rectosigmoid junction (C19), and rectum (C20). Deaths were counted when any of these codes appeared as the underlying cause of death on the death certificate. Similar epidemiologic investigations examining national mortality patterns have employed this same approach using CDC WONDER data, demonstrating its reliability for capturing temporal trends and demographic disparities in large populations [12–14]. Because only publicly available, de-identified data were used, institutional review board approval was not required, and the study followed STROBE reporting guidelines.

2.2. Data Extraction

Data were extracted from the CDC WONDER Multiple Cause of Death database (1999 – 2023) and were grouped by year, sex, race, age, census region, state, and place of death. Analyses were restricted to U.S. residents. Race and ethnicity were categorized as non-Hispanic (NH) White, NH Black, Hispanic/Latino, NH American Indian/Alaska Native, and NH Asian or Pacific Islander. Due to suppression of cells with small counts in the database, observations with less than the minimum reportable number were excluded from detailed trend analyses to prevent unreliable estimates. Geographic variables included U.S. Census Bureau regions (Northeast, Midwest, South, and West). Urban – rural status was defined using the NCHS 2013 six-level county classification scheme and dichotomized as metropolitan (large central metro, large fringe metro, medium metro, and small metro) versus non-metropolitan (micropolitan and noncore counties). Urban – rural analyses were restricted to 1999 – 2020 due to changes and incomplete availability of stratified NCHS urbanization data in subsequent years, which limit temporal comparability beyond this period. Place-of-death categories included medical facilities, home, hospice facilities, and nursing home/long-term care settings. Age was stratified into 3 groups (25 – 44, 45 – 64, and 65 years and older).

2.3. Statistical Analysis

Crude mortality rates (CMRs) and age-adjusted mortality rates (AAMRs) were calculated per 100,000 population using the 2000 U.S. standard population for age adjustment. AAMRs were used for overall and subgroup comparisons to account for differences in age distributions across populations and over time, whereas CMRs were used for age-specific analyses because age adjustment is not applicable within fixed age strata. Crude rates were computed by dividing annual colorectal cancer deaths by corresponding population estimates.

Trends in AAMRs over time were examined using the Joinpoint Regression Program (version 5.4.0.0, National Cancer Institute). Log-linear models (natural logarithm of AAMRs) were used. Standard errors for AAMRs were derived from CDC WONDER using the gamma method and incorporated into Joinpoint using the default heteroscedastic error model with weighted least squares. The autocorrelation option was not enabled. Default program settings were used for minimum segment length and model selection parameters, with a maximum of three joinpoints specified. This method detects statistically significant changes in trend direction and estimates the Annual Percent Change (APC) for each segment. This software fits log-linear regression models and identifies statistically significant temporal shifts across the study period. The Monte Carlo permutation method was used for model selection, allowing up to three joinpoints. Statistical significance of the APC was assessed using t-tests, and the Average Annual Percent Change (AAPC) was calculated to summarize overall trends. All results were reported with 95% confidence intervals. Analyses involving smaller racial/ethnic populations, particularly non-Hispanic Asian or Pacific Islander individuals, were interpreted cautiously due to potential statistical instability arising from smaller death counts, which may contribute to apparent short-term fluctuations rather than true epidemiologic changes.

3. Results

3.1. Overall mortality trends

Throughout the study timeframe, from 1999–2023, a total of 1,551,550 deaths were attributed to CRC in the United States. The majority of the deaths occurred at the deceased's residence (40.73%), followed by medical facilities (29.45%), nursing homes/long-term care facilities (16.92%), and hospice settings (7.44%). A small proportion of deaths occurred at other locations (5.21%), while some

deaths had an unknown place of death (0.24%) (Supplemental Tables 1, 2).

The overall AAMR declined from 38.23 in 1999 to 22.93 in 2023 (AAPC: -2.14; 95% CI: -2.39 to -1.88; $p < 0.01$). Trends over different time period showed that the AAMR decreased from 38.23 in 1999 to 25.67 in 2013 (APC: -2.97; 95% CI: -3.13 to -2.82; $p < 0.01$), followed by a continued decline to 22.78 in 2019 (APC: -1.73; 95% CI: -2.51 to -0.95; $p = 0.002$), and a non-significant increase to 22.93 in 2023 (APC: 0.23; 95% CI: -0.82 to 1.30; $p = 0.65$) **(Supplemental Tables 3) and (Figure 1)**.

3.2. Trends in mortality by sex

Overall, men (deaths: 807,428; AAMR: 34.74) showed higher mortality rates than women (deaths: 744,122; AAMR: 23.79). Overall, the AAMR declined in both sexes between 1999 and 2023; 31.98 to 19.09 (AAPC: -2.16; 95% CI: -2.47 to -1.84; $p < 0.01$) among women, as compared to 47.46 to 27.43 (AAPC: -2.31; 95% CI: -2.45 to -2.16; $p < 0.01$) among men.

Trends over different time period showed that AAMR among women decreased significantly from 31.98 in 1999 to 21.31 in 2013 (APC: -3.00; 95% CI: -3.18 to -2.82; $p < 0.01$), followed by a continued marked decrease to 18.88 in 2019 (APC: -1.85; 95% CI: -2.79 to -0.90; $p = 0.008$), and a non-significant increase to 19.09 in 2023 (APC: 0.37; 95% CI: -1.01 to 1.76; $p = 0.58$). Among men, AAMR showed a significant decline from 47.46 in 1999 to 29.74 in 2015 (APC: -3.08; 95% CI: -3.21 to -2.94; $p < 0.01$), followed by a subsequent marked decrease, reaching 27.43 in 2023 (APC: -0.75; 95% CI: -1.14 to -0.35; $p = 0.009$) **(Supplemental Tables 1, 3, 4)** and **(Figure 1)**.

3.3. Racial trends

Among racial groups, the highest number of deaths were recorded among NH White individuals (1,305,509), followed by NH Black/African American individuals (195,008), Hispanic/Latino individuals (93,645), NH Asian/Pacific Islander individuals (41,365), and NH American Indian/Alaska Native individuals (8,331). All racial groups observed a notable decrease in AAMR from 1999 to 2023; 25.17 to 16.63 (AAPC: -1.74; 95% CI: -2.08 to -1.39; $p < 0.01$) among NH American Indians, 21.62 to 14.91 (AAPC: -1.74; 95% CI: -2.08 to -1.39; $p < 0.01$) among NH Asians, 50.51 to 27.68 (AAPC: -2.54; 95% CI: -2.79 to -2.29; $p < 0.01$) among NH Black individuals, 37.46 to 23.05 (AAPC: -2.03; 95% CI: -2.28 to -1.77; $p < 0.01$) among NH Whites, and 25.30 to 18.43 (AAPC: -1.40; 95% CI: -1.60 to -1.20; $p < 0.01$) among Hispanics. The overall AAMR was highest among NH Black individuals (37.34), followed by NH Whites (27.99), Hispanics (21.18), NH American Indians (20.83), and NH Asians (18.72).

Trends over time periods revealed that the AAMR among NH Asians showed variation; an initial increase from 21.62 in 1999 to 23.98 in 2001 (APC: 3.75; 95% CI: -6.87 to 15.59; $p = 0.48$), a steep yet significant decrease to 15.21 in 2018 (APC: -2.53; 95% CI: -2.84 to -2.21; $p < 0.01$), a steady yet non-significant increase to 16.47 in 2021 (APC: 2.30; 95% CI: -4.62 to 9.73; $p = 0.50$), and a downward trend, reaching 14.91 in 2023 (APC: -3.79; 95% CI: -10.17 to 3.03; $p = 0.25$). No joinpoints were detected for NH Americans.

NH Black individuals observed a marked decrease in AAMR from 50.51 in 1999 to 29.01 in 2018 (APC: -2.98; 95% CI: -3.13 to -2.83; $p < 0.01$), followed by a continued non-significant decrease to 27.68 in 2023 (APC: -0.86; 95% CI: -2.02 to 0.32; $p = 0.14$). NH White individuals showed a marked decrease in AAMR from 37.46 in 1999 to 25.60 in 2012 (APC: -3.02; 95% CI: -3.20 to -2.84; $p < 0.01$), followed by a continued significant decrease to 22.53 in 2019 (APC: -1.72; 95% CI: -2.33 to -1.09; $p = 0.002$), and a non-significant increase to 23.05 in 2023 (APC: 0.70; 95% CI: -0.43 to 1.85; $p = 0.21$). AAMR among Hispanics showed a steep yet significant decline from 25.30 in 1999 to 18.51 in 2016 (APC: -1.96; 95% CI: -2.16 to -1.77; $p < 0.01$), subsequently decreasing non-significantly 18.43 in 2023 (APC: -0.03; 95% CI: -0.60 to 0.55; $p = 0.93$) **(Supplemental Tables 1, 5)** and **(Figure 2)**.

3.4. Regional trends

The highest number of deaths occurred in the Southern region (575,476), followed by the Midwest (368,876), the Northeast (304,639), and the West (304,559). All regions experienced significant decreases in AAMR throughout the study period; 41.96 to 20.37 (AAPC: -2.99; 95% CI: -3.48 to -2.50; $p < 0.01$) in the Northeast, 41.01 to 23.63 (AAPC: -2.27; 95% CI: -2.45 to -2.09; $p < 0.01$) in the Midwest, 36.64 to 24.56 (AAPC: -1.73; 95% CI: -2.05 to -1.41; $p < 0.01$) in the South, and 33.71 to 21.43 (AAPC: -1.91; 95% CI: -2.12 to -1.70; $p < 0.01$) in the West. Overall AAMRs were higher in the Midwest (30.05), followed by the South (28.78), the Northeast (28.66), and the West (26.00).

Time specific analysis showed that AAMR in the Northeast decreased significantly from 41.96 in 1999 to 38.70 in 2002 (APC: -2.84; 95% CI: -4.49 to -1.16; $p = 0.003$), followed by a continued marked decrease to 32.95 in 2005 (APC: -5.04; 95% CI: -8.48 to -1.54; $p = 0.008$), a steep decline to 21.85 in 2018 (APC: -3.15; 95% CI: -3.37 to -2.92; $p < 0.01$), and a steady yet significant decrease to 20.37 in 2023 (APC: -1.43; 95% CI: -2.37 to -0.48; $p = 0.006$). AAMR in the Midwest decreased significantly from 41.01 in 1999 to 25.89 in 2015 (APC: -2.97; 95% CI: -3.12 to -2.81; $p < 0.01$), followed by a continued downward trend to 23.63 in 2023 (APC: -0.85; 95% CI: -1.34 to -0.37; $p = 0.002$).

AAMR in the South declined significantly from 36.64 in 1999 to 26.12 in 2013 (APC: -2.63; 95% CI: -2.82 to -2.43; $p < 0.01$), followed by a continued decrease to 23.87 in 2019 (APC: -1.33; 95% CI: -2.26 to -0.39; $p = 0.008$), and a non-significant increase to 24.56 in 2023 (APC: 0.86; 95% CI: -0.48 to 2.22; $p = 0.19$). The Western region experienced a significant decrease from 33.71 in 1999 to 22.18 in 2016 (APC: -2.65; 95% CI: -2.82 to -2.48; $p < 0.01$), followed by a continued non-significant decrease, reaching 21.43 in 2023 (APC: -0.09; 95% CI: -0.73 to 0.56; $p = 0.78$) **(Supplemental Tables 3, 6)** and **(Figure 3)**.

3.5. Mortality trends by urbanization

Between 1999 and 2020, metropolitan areas accounted for greater mortality (1,096,992 deaths) as compared to non-metropolitan areas (267,125 deaths). However, the overall AAMR was higher in non-metropolitan areas (32.08) as compared to metropolitan areas (27.81). From 1999 to 2020, metropolitan areas observed a decrease in AAMR from 37.93 to 22.03 (AAPC: -2.70; 95% CI: -2.86 to -2.55; $p < 0.01$), as compared to non-metropolitan areas, where AAMR decreased from 39.68 to 27.78 (AAPC: -1.77; 95% CI: -1.99 to -1.55; $p < 0.01$).

Segmented trend analysis (1999–2020) showed that AAMR in metropolitan areas showed a significant decline from 37.93 in 1999 to 24.88 in 2013 (APC: -3.14; 95% CI: -3.29 to -3.00; $p < 0.01$), followed by a continued downward trend, reaching 22.03 in 2020 (APC: -1.82; 95% CI: -2.24 to -1.39; $p < 0.01$). In non-metropolitan areas, AAMR showed a marked decrease from 39.68 in 1999 to 28.61 in 2014 (APC: -2.20; 95% CI: -2.37 to -2.03; $p < 0.01$), followed by a non-significant decrease to 27.78 in 2020 (APC: -0.68; 95% CI: -1.39 to 0.04; $p = 0.06$) **(Supplemental Tables 3, 7)** and **(Figure 4)**.

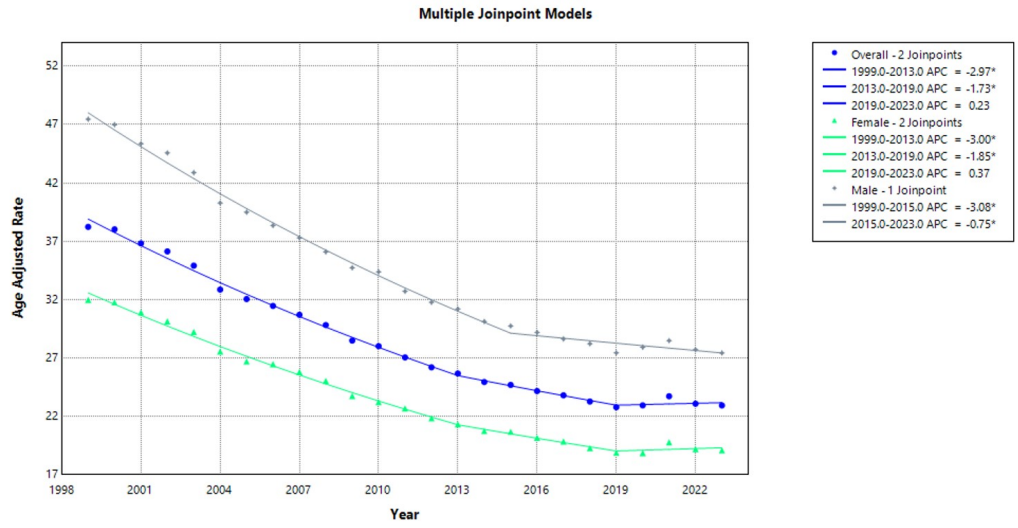

Figure 1: Overall and Sex-Stratified Colorectal Cancer-Related AAMRs per 100,000 in Adults in the United States, 1999-2023.

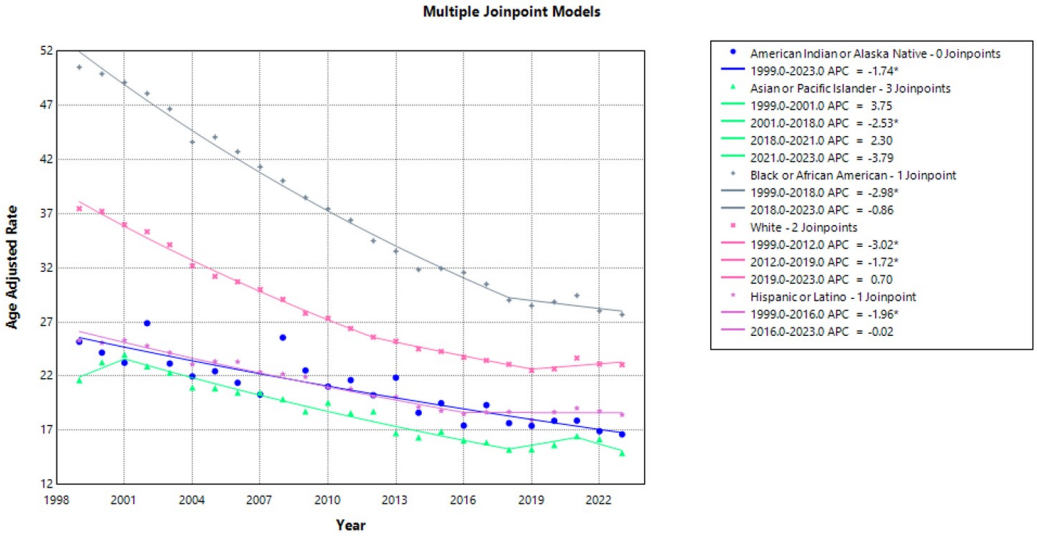

Figure 2: Colorectal Cancer-Related AAMRs per 100,000 Stratified by Race in Adults in the United States, 1999-2023.

3.6. Age-specific mortality trends

Older adults accounted for the greatest mortality (deaths: 1,138,374; overall CMR: 107.87), followed by middle-aged adults (deaths: 369,331; overall CMR: 19.06), and young adults (deaths: 43,845; overall CMR: 2.07). Throughout the study period, from 1999–2023, young adults showed an increase in CMR from 1.95 to 2.36 (AAPC: 0.88; 95% CI: 0.51 to 1.26; $p = 0.003$). In contrast, other age groups showed declines in CMR across the same period; a non-significant overall decline from 21.01 to 19.86 (AAPC: -0.25; 95% CI: -0.52 to 0.02; $p = 0.07$) among middle-aged adults, and a significant drop from 152.83 to 74.58 (AAPC: -2.97; 95% CI: -3.20 to -2.74; $p < 0.01$) among older adults. Trends over time periods showed that the CMR among young adults increased significantly from 1.95 in 1999 to 2.02 in 2019 (APC: 0.44; 95% CI: 0.23 to 0.65; $p = 0.003$), followed by a continued rise, reaching 2.36 in 2023 (APC: 3.15; 95% CI: 0.98 to 5.37; $p = 0.006$). Among middle-aged adults, CMR decreased significantly from 21.01 in 1999 to 17.80 in 2005 (APC: -2.64; 95% CI: -3.36 to -1.92; $p = 0.001$), followed by a marked increase to 18.83 in 2018 (APC: 0.28; 95% CI: 0.04 to 0.52; $p = 0.03$), and a continued rise to 19.86 in 2023 (APC: 1.30; 95% CI: 0.41 to 2.20; $p = 0.007$). Older adults experienced significant decreases in CMR throughout the study timeframe; a decrease from 152.83 in 1999 to 141.35 in 2003 (APC: -2.20; 95% CI: -3.21 to -1.17; $p = 0.003$), which continued to 83.15 in 2017 (APC: -3.85; 95% CI: -4.03 to -3.67; $p < 0.01$), and then decreased to 74.58 in 2023 (APC: -1.44; 95% CI: -2.03 to -0.84; $p = 0.001$) **(Supplemental Tables 3, 8)** and **(Figure 5)**.

4. Discussion

This national study demonstrates an overall decline in mortality attributed to CRC among adult individuals in the U.S. across 25 years. The analysis shows a significant downward trend in mortality rates due to CRC between 1999 and 2019, across most subgroups, including both sexes, racial groups, geographic locations, and levels of urbanization. However, this favorable trend has attenuated in recent years, with AAMRs plateauing after 2019. In contrast, young

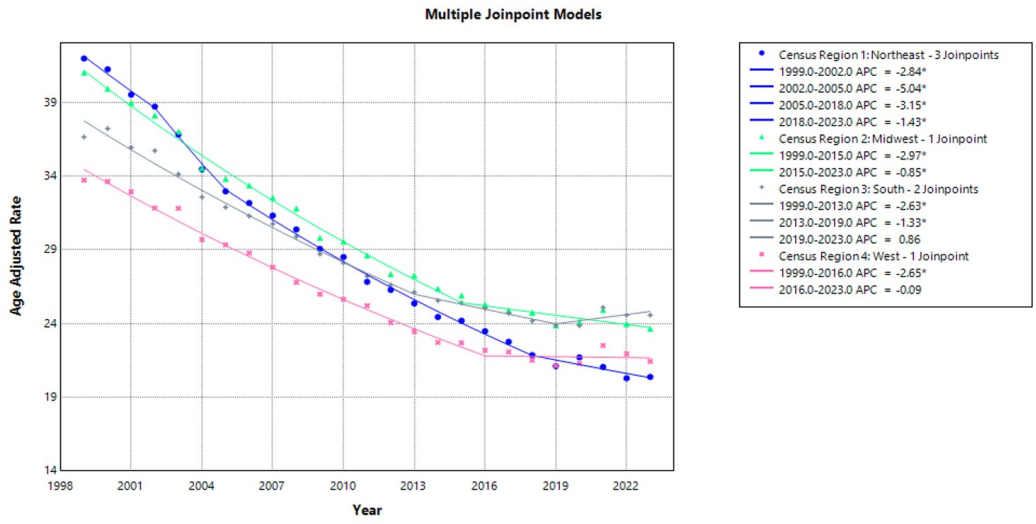

Figure 3: Colorectal Cancer-Related AAMRs per 100,000 Stratified by Census Region in Adults in the United States, 1999-2023.

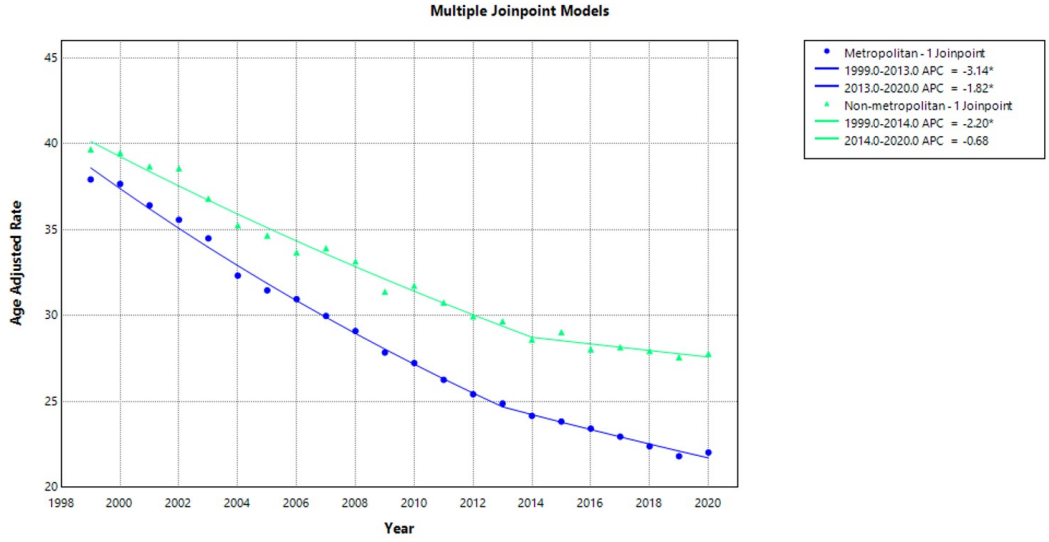

Figure 4: Colorectal Cancer-Related AAMRs per 100,000 Stratified by Urban-Rural status in Adults in the United States, 1999-2020.

adults experienced a persistent increase in mortality throughout the study period, with a notable acceleration from 2019 to 2023. Furthermore, mortality among middle-aged adults initially declined until 2005, but subsequently rebounded, while older adults continued to exhibit significant reductions. Additionally, men and NH Black individuals exhibited the highest burden. Variations across regions are also evident, with the Midwest showing greater AAMRs compared to smaller rates reported from the Western states. Higher AAMRs were observed in non-metropolitan areas, pointing to structural and geographic challenges. Notably, we report that the predominance of deaths was at home. While older adults aged 65 and older still represent the larger share of CRC deaths, young adults had a sustained rise in CMR, suggesting an emerging shift in age-specific mortality patterns.

The observed decline in mortality is consistent with parallel declines in CRC incidence among older adults. These trends may also reflect the effects of screening and early detection, though our data do not measure individual screening or treatment [15, 16]. Moreover, survival has improved in recent years, which may relate to advances in therapy, but our dataset cannot directly assess treatment effects. This is in agreement with results from a 2004–2019 retrospective cohort study conducted in the U.S., which depicted marked improvements in overall survival after 2012 among patients with metastatic CRC [17]. Collectively, all these tools may have contributed to the decrease in overall CRC deaths; however, they represent plausible explanations that warrant linkage to screening and treatment data. The down trajectory was most significant between 1999 and 2013, followed by a slower decline. However, after 2019, there was a slight, non-significant increase in the mortality pattern, possibly attributable to rising incidence in younger adults, and substantial disruptions in healthcare during the COVID-19 pandemic. Subsequently, CRC screening rates declined sharply, with an over 50% reduction in mid-2020 compared with 2019 [17]. Although CRC screening rates declined during the pandemic, the long lag from precursor lesions to cancer-related deaths suggests these disruptions are unlikely to fully explain observed mortality patterns from 2019 to 2023. Short-term

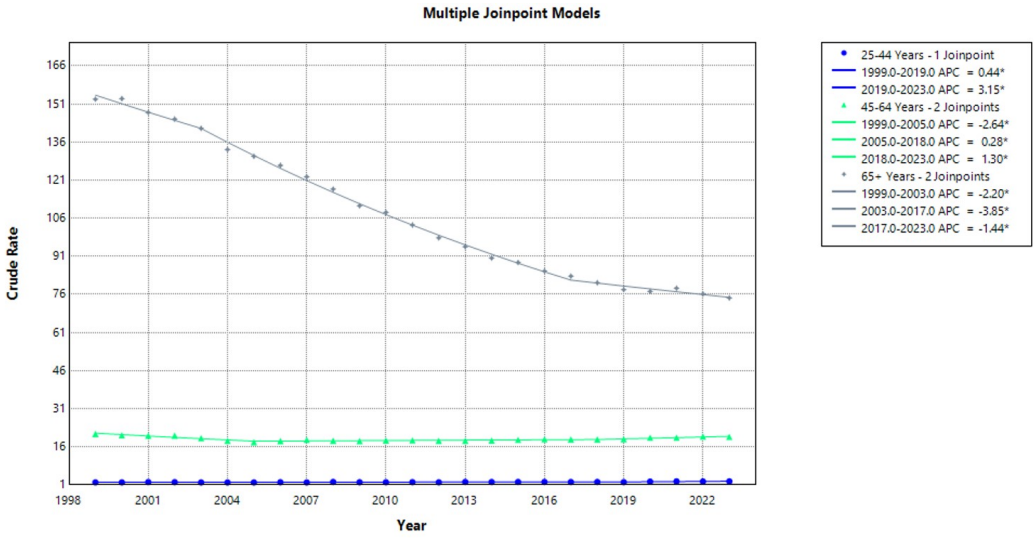

Figure 5: Colorectal Cancer-Related CMRs per 100,000 Stratified by Age in Adults in the United States, 1999-2023.

fluctuations may reflect multiple factors, which cannot be directly measured in this dataset [18, 19]. Whereas the impact of reduced screening is expected to emerge in future trends, with modeling studies projecting a 1.9% and 2.4% increase in mortality over 2020 – 2030 in countries such as Canada and Australia, respectively, driven by COVID-19 – related reductions in CRC screening, diagnosis, and treatment in 2020 [20]. However, by 2023, CRC screening in the U.S. had rebounded beyond pre-pandemic levels, although mostly confined to individuals with higher socioeconomic status, including those with higher education and private or Medicare insurance [21].

The sex-specific disparity observed from 1999 to 2023, characterized by higher mortality rates in males, is consistent with findings from prior studies [22, 23]. This pattern likely reflects an interplay of biological and environmental differences, alongside variable behavioral factors such as smoking, heavy alcohol consumption, unhealthy diet, physical inactivity, and obesity, all causing men to face a higher susceptibility to CRC [24]. Male sex is an independent risk factor for CRC, whereas estrogen enhances anti-tumor immunity and promotes a more favorable gut microbiota, acting through its estrogen receptor beta (ERβ) anti-proliferative and pro-apoptotic effects implicated in CRC risk reduction [25]. Additionally, lower circulating estrogen levels together with higher testosterone have been associated with a greater incidence of microsatellite-unstable CRC in males [26]. Furthermore, differences in CRC screening adherence may contribute to this pattern, as in 2021, men had a lower up-to-date CRC screening uptake of 56% compared with 60% among women, both aged 45 to 75 [15]. Although males continue to bear a higher mortality burden, mortality rates have decreased in both sexes, a trend that may be consistent with differences in screening uptake, risk factors, and treatment patterns, which are not directly measured in this dataset [27, 28].

Our findings also highlighted prominent racial disparities, with the highest AAMR noted among NH Black individuals. Other studies have reported similar findings, potentially stemming from differences in health insurance coverage, explaining nearly half of the poorer outcomes seen among black populations [29]. Socioeconomic adversity and aggressive biologic characteristics with higher metastatic potential or higher tumor grades may also contribute to the race-stratified trend observed in our study [30, 31]. Interestingly, one study states that worse outcomes persist even in highly educated and insured Black individuals in higher-income communities, underscoring the multifactorial nature of this disparity [32]. NH Asian or Pacific Islander patients had the lowest AAMR across the study period. In contrast, NH Black individuals had the highest mortality rates, followed by NH White individuals, NH American Indian/Alaska Native individuals, and Hispanic or Latino individuals, the latter showing a continued reduction in AAMR throughout the study period. Despite having the lowest mortality rates overall, NH Asian/Pacific Islanders demonstrated a transient increase in mortality between 1999 and 2001. Moreover, NH Black individuals exhibited the largest reduction in AAMRs over time, reflecting improvements in addressing contributors to this disparity.

Our analysis found significant geographic differences, with the Midwest exhibiting the highest AAMR and the West reporting the lowest, as noted in earlier studies [33]. Although decreases in AAMR were observed nationwide, the Northeast experienced the steepest decline, reaching the lowest recent mortality levels. In this regard, subjects living in the Northeastern states achieved the highest screening prevalence according to data from the 2020 Behavioral Risk Factor Surveillance System, a factor that may partially explain the region's comparatively reduced mortality burden [15]. Conversely, the Southern states showed the smallest reduction in AAMR, while displaying a fluctuating pattern, with a non-significant upward trend following a period of decline from 1999 to 2019. The underlying reasons behind the high AAMRs observed in the Midwest and the South may include the higher prevalence of risk factors such as unhealthy diet, smoking, excess body weight, physical inactivity, and diabetes, as well as the greater socioeconomic disadvantage, reduced access to screening centers and specialty care, especially in large rural populations present in these regions [17]. This study highlighted that the Midwest has the highest mortality, which aligns with the presence of the previous risk factors; for example, obesity rates were highest in the Midwest (35.9%), followed by the South (34.5%) in 2024 [34].

A notable finding in this study was the greater proportion of deaths taking place at home rather than in hospitals, suggesting a growing emphasis on patient-centered end-of-life care [35]. The prevalence of home-based deaths may be driven by state-level palliative care legislation that increases access to home and hospice services,

aligning with the preferences of nearly 85% U.S. patients who report favoring to die at home [36]. Still, lower socioeconomic status restricts access to hospice or home-based palliative care, causing gaps between the preferred and actual place of death [37]. A U.S. study showed that the place of death varies by age and geography. Younger cancer patients (aged 15 – 24 years) were consistently more likely to die in a hospital than those aged ≥85 years (60.3% vs 25.7% in 1999 and 50.9% vs 15.0% in 2015). Additionally, patients living in large central metropolitan areas were the most likely to experience hospital death [38].

Mortality trends of CRC revealed considerable urban-rural disparities between 1999 and 2020. Residents of rural areas experienced higher AAMR compared with those in metropolitan regions, consistent with previous evidence suggesting that inequity in socioeconomic status, transportation issues, and modifiable risk factors, most notably obesity and tobacco use, represent potential contributors to the observed heterogeneity in CRC-related rates [39, 40]. Individuals living in rural areas often face limited access to medical and surgical oncology services, which in turn can result in delayed diagnosis and later cancer stages [41]. However, another study reported that patients with CRC residing in rural areas do not consistently exhibit higher rates of late-stage presentation [42]. Further contributing to the heavy CRC burden within rural communities is the decreased prevalence of CRC screening. Certain barriers can hinder access to CRC early detection screening for rural subjects, with the most frequently reported barriers being financial constraints, lack of insurance coverage, limited medical literacy, and long travel distances [43–45]. Evidence has indicated that the introduction of the Affordable Care Act (ACA) was associated with higher CRC screening rates by reducing cost-related obstacles [46]. Compared with non-metropolitan regions, metropolitan areas experienced a sharper decline in CRC mortality, with both settings exhibiting a significant downward trend. Consequently, this widens the gap between rural and urban areas. This necessitates immediate modifications in health policy actions to expand Medicaid-funded CRC screening and timely treatment services to socioeconomically disadvantaged populations in rural areas.

Age stratification of CRC mortality revealed markedly divergent trends across the study period. Adults aged 65 years and older had the highest rate of CRC-related mortality. Moreover, older adults experienced substantial decreases in CRC mortality throughout 1999 to 2023; meanwhile, the decline slowed after 2017, mirroring previously published evidence that attributes the continued but decelerating reductions in older adults to higher access to screening programs, reduced risk factors such as smoking, and improved treatment outcomes [47, 48]. In contrast, adults aged 45 to 64 years exhibited an early downswing, followed by a plateau, and then transitioned to a final upward trajectory up to 2023. This result aligns with trends reported in earlier studies, highlighting a growing burden of early-onset CRC (EOCRC), though the rise of EOCRC partly contributes to the mortality increase noted in middle-aged adults, as EOCRC affects adults under 50, and accompanied by the lowest screening uptake in those aged 45-49 years at only 20% compared with 80% in adults aged 65-74 years, as recently reported by the American Cancer Society [15, 49]. The reasons behind the rising incidence of EOCRC over the past four decades remain unclear. Possible explanations include gut microbial dysbiosis from early-life antibiotic exposure, dietary patterns high in red meat and low in fiber, and higher rates of obesity and sedentary behavior [50]. However, this is in contrast with evidence from a retrospective study describing a nonsignificant link between obesity and EOCRC [51]. As a result, an urgent need remains for research to identify other emerging determinants influencing EOCRC risk.

The youngest cohort (25-44 years) is especially noteworthy, given that they recorded the greatest escalation in CMR. Despite continued overall declines in ages 45 and above, CRC diagnoses are increasing disproportionately at a younger age. Projections suggest that by 2030, colon cancer incidence among younger adults aged 20-34 may approach a two-fold increase, while rectal cancer in this age group may exceed the two-fold rise [52]. These findings demonstrate favorable CRC trends in older adults since 1999, with slower declining rates in more recent years. Among younger adults CRC mortality is rising, warranting further attention. Among younger adults, the upward trend in CRC-attributed mortality coincides with lower screening uptake and lifestyle risk factors, though we cannot assess individual-level determinants [53]. EOCRC cases frequently present at more advanced stages, with more than half diagnosed at stage III or IV [54]. Moreover, younger patients are also more likely to have unfavorable pathological tumor features, including poor differentiation, mucinous histology, and signet-ring cell morphology [55]. Still, the decision to initiate CRC screening at younger ages requires thoughtful assessment of the potential benefits and risks. Evidence remains mixed regarding the net balance of early screening subjects under 45 years, because of concerns about procedure-related complications, the cumulative lifetime number of colonoscopies, and the possibility of overdiagnosis. Accordingly, strengthening public awareness, as both healthcare providers and symptomatic younger adults should recognize the potential risk, and encouraging cost-effective early routine screening should be adopted to counter the rising mortality rates in the younger age group.

5. Limitations

Our study has some limitations that should be considered. A key limitation of this study is the potential risk of misclassification bias of CRC-related deaths due to inaccuracies in death certificate documentation, which may result in underestimation of mortality rates. Given that the CDC WONDER database relies on accurate reporting and ICD-10 coding of death certificates. An important limitation is that rural – urban stratification in the CDC WONDER database is only available through 2020, which restricts subgroup analyses in later years and may potentially underestimate recent changes in geographic disparities in mortality. Our study is limited by the broad coded classification of the place of death variable and by changes in care delivery and documentation practices during the study period that may have influenced the observed patterns but could not be assessed in this study. Furthermore, the data presented from the CDC WONDER platform are based on the underlying cause of death, limiting the ability to account for certain variables and comorbidities that may influence mortality patterns. This population-level database contains publicly available data that lacks individual-level risk factors such as family history, screening adherence, tumor stage, or treatment details, including prior chemotherapy or radiation. The absence of these clinical and behavioral confounding variables restricts our capacity to fully interpret the observed disparities. Therefore, future studies should work on a more in-depth analysis of cancer registries to gain additional insights into CRC mortality, even though not all the mentioned variables can be captured in a single study. Nevertheless, the use of the CDC WONDER comprehensive data set provides standardized, nationally representative mortality data. Additionally, the inclusion of the most recent data spanning 1999–2023 provides a timeframe for analyzing long-term mortality trends. Lastly, stratifying the data by age, sex, race, and urbanization offers a greater insight into CRC mortality disparities, enabling the identification of underrepresented groups in need of tailored interventions, such as the young adults, as well as recognizing the

disproportionately affected populations, including NH blacks, men, the elderly, and residents of rural and midwestern regions.

6. Conclusion

Based on this retrospective analysis, CRC mortality has generally declined across U.S. adults over the past 25 years, with the exception of young adults, who experienced rising rates. Disparities persist across geographic, age, and sociodemographic groups, particularly in non-metropolitan areas, among younger adults, men, and NH Black individuals. Public health and health-system strategies aimed at improving access to CRC screening, timely evaluation of symptoms in younger adults, and reducing barriers in rural and underserved regions may help address these observed disparities.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Ethical approval

No ethical approval was required for the study.

Large Language Model

None.

Authors' Contributions

MT and AAI Conceptualization, Writing-original draft, Writing-review and editing. MRS, MRF, and SE Formal Analysis, Writing-original draft. AH Data curation, Writing-original draft. RS Formal Analysis. MN, HA, and MMA Writing-original draft. AAM Data Extraction and data curation. SF Writing-original draft. ATE Writing-review and editing. AE Writing-review and editing. AA and MFH Writing – review and editing, Validation, Supervision.

Data Availability

The data that support the findings of this study are openly available in CDC-WONDER at https://wonder.cdc.gov/. The data supporting the findings of this study were obtained from the CDC WONDER online database (Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research). Further inquiries can be directed to the corresponding author.

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