Research Article

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Colorectal Cancer

# The impact of young adult colorectal cancer: incidence and trends in Colorado

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## Practice points

- The absolute incidence of colorectal cancer continues to fall in the state of Colorado.
- However, the incidence is rising in individuals under the age of 50, particularly males.
- There is a trend toward later stage disease at diagnosis in young adults.
- The overall cause of rising incidence in young adults is still unknown, but there are multiple known risk factors that may be contributing to this trend, including genetic, environmental, or lifestyle-based.
- Further analysis is warranted into potential biologic difference between tumors in younger and older patients.

**Aim:**Far less is known about colorectal cancer (CRC) incidence in individuals under the age of 50. This study examined CRC incidence in order to better understand the changing CRC population. **Methods:** This study analyzed 39,525 CRC cases from the Colorado Central Cancer Registry from 1992 through 2013. Age-adjusted incidence, observed and relative 5-year survival, and estimated annual percentage change was analyzed. **Results:** Age-adjusted rates averaging 1.7% per year were observed in the under-50 population, while falling on average 4.3% per year ($p < 0.05$) in the over-50 population. Average-adjusted incidence rose in males under 50 by 2.7% per year ($p < 0.05$). **Conclusion:** The absolute incidence of CRC continues to fall in Colorado, however incidence is rising in individuals under 50, particularly males.

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**Keywords:** age • cancer registry • colon cancer • colorectal cancer • incidence • rectal cancer • young adults

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide (10.0 and 9.2% of total, respectively). Global incidence is estimated at 1,400,000 cases annually, with 694,000 deaths, according to International Agency for Research on Cancer 2012 data [1]. Thus, CRC represents an important public health issue. The surveillance, epidemiology and end-results (SEER) program estimates that there will be 132,700 new cases and 49,700 deaths in the USA in 2015 due to CRC [2]. In Colorado, CRC accounted for 1744 cases in 2012 alone, and had an incidence rate of 33.4 new cases per 100,000 population [3].

The overall incidence of CRC in the USA is decreasing. From 2007 through 2011, incidence decreased 3.6% on average annually, irrespective of gender, a trend which continues back as far as 1992 [4]. This trend is seen in Colorado as well, with age-adjusted incidence decreasing from 54.1 per 100,000 in 1990 to 33.4 in 2012 [3]. US death rates also continue to drop overall, with average annual rates falling 2.6% for males and 3.0% for females since 1992 [4]. Perhaps most noteworthy is that 5-year survival rates in the USA have improved from 51% in 1975 to 65% in 2010 [2], indicating overall improvement in the screening, prevention and treatment of CRC.

Patients 50 years of age and older have been well-described in the literature [5], but significantly less research has been performed in patients diagnosed as adolescents and young adults, potentially due to US Preventive Services Task Force and National Comprehensive Cancer Network guidelines advising screening starting at age 50 for individuals of average risk [6,7]. Young adult (YA) oncology is a rapidly growing field that has emerged out of the

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realization that persons diagnosed with cancer between 18 and 49 years of age have not benefited as much as older individuals from improving survival rates over the past two decades [8]. Similarly, although age was not shown to be an independent prognostic factor for CRC [9], a retrospective review found a significantly higher proportion of stage III–IV tumors in YAs (69.3%) compared with older adults (46.4%) [9]. Additionally, there is evidence of greater family disruption and loss of productive years in YA patients, along with unique concerns such as fertility that are not as prevalent in older patients [10]. Clinically, YAs reported distinctly different symptom severity, symptom interference and variations over time than older patients [11], further illustrating previously unquantified disease permutations.

There is currently no consensus in the literature regarding the definition of young-onset CRC; however the rising incidence in adolescents and YAs has recently attracted increased attention from physicians, public health officials and investigators [5,12,13]. Although the traditional paradigm of CRC tends to center around environmental factors such as increased red meat intake and exposure to carcinogens [14], there is evidence of a higher prevalence of genetic risk factors such as Lynch syndrome and familial adenomatous polyposis in YA CRC cases [5]. Additionally, as overall CRC incidence has declined, disparities between racial and ethnic groups have been revealed, as well as variations in race-specific mortality rates [12]. Several datasets have indicated that age-adjusted incidence and mortality rates are highest among African–Americans and lowest among Hispanic and Asian populations [1,2,12].

The Colorado Central Cancer Registry (CCCR), a dataset novel to the analysis of CRC in YA populations [3], hypothesized that we would observe similar trends as those previously documented in the USA [4,13] and other state-specific databases [12] despite low overall incidence of CRCs in YAs. Specifically, we hypothesized that we would observe overall incidence of CRCs declining in Colorado, but that incidence would be increasing in populations under 50 years old, incidence would be higher in males than in females, and that Asian and Hispanic populations would exhibit lower incidence. Of note, Colorado's population differs from the general US population in that it has a greater proportion of individuals identifying as white (83–75%, respectively) and Hispanic (17–12.5%, respectively), while having a lower population of African–Americans (4–12%) and Asians (2–4%) [15]. Additionally, Colorado regularly ranks among the healthiest states in the USA and had the lowest levels of obesity and physical inactivity in 2015 [16]. We analyzed age-adjusted incidence rates of CRC in the state of Colorado from 1992 through 2013, stratifying by age, sex, race/ethnicity and tumor stage at diagnosis.

## Methods

Cases and associated data were obtained from the CCCR, from 1992 through 2013 (n = 39,525). The CCCR is essentially complete statewide, with completeness estimates from 96 to 100% year to year [3]. The CCCR collects data for all reportable cancers and for each case collects all National Program for Cancer Registries-required data items as well as many additional items. All data are exchanged in the appropriate national standard data exchange formats according to the North American Association of Central Cancer Registries. The data are entered at the hospital by a trained certified tumor registrar (CTR), who abstracts the data from medical charts and utilizes data checking software. These data are then checked again for quality at the CCCR, where all staff involved are CTRs or CTR-eligible. Additionally, quality control audits occur regularly to assure quality data, and quarterly meetings are held between key CCCR and hospital staff to discuss data collection and data quality issues.

Data items include tumor type, stage of disease at diagnosis, initial treatments, age, sex, race and residence. The CCCR is novel to the analysis of CRC in YA populations, and additional statistics are updated regularly [3]. We examined cases from the four largest race/ethnicities in Colorado: Caucasian, African–American, Hispanic and Asian. Analysis of individuals of native American and unknown ancestries was not performed due to the small number of cases, but these individuals were included in analyses that were not ethnicity-dependent.

Stage of disease at the time of cancer diagnosis was defined via the SEER summary stage: *in situ*, localized, regional and distant spread. Tumor origin was determined based on ICD-O-3 codes C180–209 and C260, which cover the colorectal anatomical subsites. These included tumors of the cecum (C180), appendix (C181), hepatic flexure (C183), splenic flexure (C185), rectosigmoid junction (C199), rectum (C209), large intestine NOS (C188–189, C260), and ascending (C182), transverse (C184), descending (C186), and sigmoid colon (C187). This study was considered exempt by the Colorado Multiple Institutional Review Board under 45 CFR 46.101(b)(4).

### Statistical analyses

Age was categorized into 18 age groups (0–4, 5–9,. . . 80–84 and 85+), which were utilized to determine age-specific incidence rates as well as stratify gender- and race/ethnicity-specific incidence rates. Where appropriate,

age cohorts were condensed into two groups (0–50 and 50+) to elucidate characteristics of YA CRC cases overall. Average annual age-adjusted incidence rates were calculated for each cohort per 100,000 person-years and adjusted to the 2000 US standard population by the direct method, per data from the 2000 US Census [15].

The estimated annual percent change (EAPC) is calculated by fitting a regression line to the natural logarithm of the annual incidence rates, using calendar year as a regressor variable. The EAPC assumes that the rates increased or decreased at a constant rate over the entire interval, and in those instances where at least one of the rates was zero, the linear regression was not calculated. A *t*-test with nine degrees of freedom was used to evaluate the significance of the 1992–2002 and 2003–2013 time trends, and the null hypothesis tested was that the true mean annual percent change is zero. Relative survival rates were calculated as the observed proportion of patients surviving a CRC diagnosis compared with the expected survival of a similarly aged proportion of persons in the general population, allowing for survival comparisons across different calendar years and ages. Relative survival was not calculated if the rate calculation was based on fewer than ten cases or if the standard error for that rate was greater than 10%. Data collation, survival analysis and incidence rate analysis utilized the Rocky Mountain Cancer Data System, and age-truncated (0–49 and ≥50) age-adjusted rates and EAPC analysis were programmed with Microsoft Excel. Figures were constructed using GraphPad Prism 7.

## Results

In total, 3729 cases in persons under 50 were observed among the 39,525 CRC cases in this study. The study population was primarily Caucasian (83.7%), with significant populations of Hispanics (10.9%), African–Americans (3.4%) and Asians (1.5%; Table 1). A total of 20,351and 19,174 male and female cases were identified, respectively. Mean age of diagnosis overall was 68, with Caucasians (69), Hispanics (64), African–Americans (64) and Asians (65) reporting limited variance in mean ages. The majority of tumors were classified as either local (34.4%) or regional (33.8), with nearly one in five having distant involvement at diagnosis (18.4%). Over the 1992–2013 study period, the CCCR had the following missing data percentages for CRC: gender (0.0%), race/ethnicity (0.5%) and age at diagnosis (0.0%).

Incidence in the overall population has largely fallen over the study period, and this is most clearly shown in the largest study cohort, the ≥50 age group, from 2003 through 2013 (-4.3%; $p < 0.05$; Table 2). The overall findings are largely driven by the Caucasian cohort (83.7% of the subjects), but there is a persistent significant downward trend in the ≥50 African–American cohort throughout the study period (-4.7% and -3.2%; $p < 0.05$), as well as a significant drop seen from 2003 through 2013 in the ≥50 Hispanic population (-4.6%; $p < 0.05$). These findings are juxtaposed by the annual rise of 2.5% ($p < 0.05$) in Caucasians 0–49 years of age over 2003–2013, which is directly at odds with the falling incidence seen in the Caucasian ≥50 population from 2003 through 2013 (-4.3%; $p < 0.05$). While a severe drop in incidence is seen in the Asian population of 0–49 years of age, due to the small sample size (1.5% of total population) it is difficult to infer trends in this group.

When analyzing by gender, the most striking trend is the rising incidence among males 0–49 years of age while falling incidence is observed in males ≥50 (+2.5% and −4.3% respectively, $p < 0.05$) from 2003 through 2013, especially given the comparatively flat trends across both age and gender seen from 1992 through 2002 (Table 3). This is made more striking by a relatively constant incidence rate in females 0–49 years of age (+0.6), while a falling trend similar to males ≥50 is observed in females ≥50 (−4.0%, $p < 0.05$) from 2003 through 2013.

Interestingly, a similar trend is seen when stratifying by tumor stage: a significant decrease in incidence is observed in the ≥50 population regardless of stage, however late stage diagnoses in the 0–49 age cohort is rising 2.4% annually ($p < 0.05$) from 2003 through 2013. Analyzing these trends from 1992 through 2002 helps elucidate how noteworthy the 2003–2013 trends are, as from 1992 through 2002 the incidence was comparatively flat in the 0–49 age cohort, and mixed trends were seen in the ≥50 age cohort (+2.3% and -2.6% in early and late stages, respectively; $p < 0.05$).

Analyzing the trend of age-adjusted incidence over time, rates remained overall far lower in the 0–49 age cohort than those ≥50 (Figure 1), but this does not illustrate a complete picture of CRC in Colorado. Age-adjusted incidence among 0–49 years of age trended upward, increasing from 4.8 cases per 100,000 persons/year in 1992 to 6.2 cases/100,000 in 2013. Among those ≥50 years of age, adjusted incidence decreased from 178.9 cases/100,000 to 104.9 cases/100,000 over the same study period. In both cohorts, the rate of change skewed later in the study period, with 66% of the total rate change from nadir in the 0–49 cohort coming between 2003 and 2013, and 64% of the total rate change from peak in the ≥50 cohort in the same time period.

Despite younger adults trending toward later stage disease at diagnosis (Figure 2), relative 5-year survival remained

**Table 1. Demographic and disease incidence, Colorado Central Cancer Registry: colorectal cases (1992–2013).**

| Category | Total, n (%)[†] | Caucasian, n (%) | African–American, n (%) | Hispanic, n (%) | Asian, n (%) |
|---|---|---|---|---|---|
| Total | 39,525 (100) | 33,079 (83.7) | 1332 (3.4) | 4292 (10.9) | 598 (1.5) |
| Gender: | | | | | |
| – Male | 20,351 (51.5) | 16,830 (42.6) | 705 (1.8) | 2432 (6.2) | 267 (0.7) |
| – Female | 19,174 (48.5) | 16,249 (41.1) | 627 (1.6) | 1860 (4.7) | 331 (0.8) |
| Age at diagnosis: | | | | | |
| – 0–49 | 3729 (9.4) | 3182 (8.1) | 196 (0.5) | 585 (1.5) | 83 (0.2) |
| – ≥50 | 35,796 (90.6) | 30,252 (76.5) | 1136 (2.9) | 3707 (9.4) | 515 (1.3) |
| – 0–9 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| – 10–14 | 5 (0.0) | 4 (0.0) | 0 (0.0) | 1 (0.0) | 0 (0.0) |
| – 15–19 | 18 (0.0) | 14 (0.0) | 0 (0.0) | 2 (0.0) | 2 (0.0) |
| – 20–24 | 54 (0.1) | 42 (0.1) | 1 (0.0) | 8 (0.0) | 2 (0.0) |
| – 25–29 | 133 (0.3) | 99 (0.3) | 5 (0.0) | 24 (0.0) | 4 (0.0) |
| – 30–34 | 272 (0.7) | 196 (0.5) | 17 (0.0) | 49 (0.1) | 8 (0.0) |
| – 35–39 | 524 (1.3) | 372 (0.9) | 35 (0.1) | 94 (0.2) | 14 (0.0) |
| – 40–44 | 1032 (2.6) | 796 (2.0) | 58 (0.1) | 151 (0.4) | 15 (0.0) |
| – 45–49 | 1691 (4.3) | 1304 (3.3) | 80 (0.2) | 256 (0.6) | 38 (0.1) |
| – 50–54 | 3136 (7.9) | 2454 (6.2) | 141 (0.4) | 448 (1.1) | 71 (0.2) |
| – 55–59 | 3466 (8.8) | 2709 (6.9) | 149 (0.4) | 527 (1.3) | 48 (0.1) |
| – 60–64 | 4224 (10.7) | 3415 (8.6) | 151 (0.4) | 565 (1.4) | 62 (0.2) |
| – 65–69 | 5182 (13.1) | 4308 (10.9) | 212 (0.5) | 558 (1.4) | 72 (0.2) |
| – 70–74 | 5449 (13.8) | 4600 (11.6) | 184 (0.5) | 533 (1.3) | 101 (0.3) |
| – 75–79 | 5409 (13.7) | 4681 (11.8) | 128 (0.3) | 508 (1.3) | 77 (0.2) |
| – 80–84 | 4537 (11.5) | 4076 (10.3) | 98 (0.2) | 305 (0.8) | 45 (0.1) |
| – 85+ | 4393 (11.1) | 4009 (10.1) | 73 (0.2) | 263 (0.7) | 39 (0.1) |
| Tumor stage at diagnosis: | | | | | |
| – *In situ* | 2740 (6.9) | 2317 (5.9) | 110 (0.3) | 261 (0.7) | 36 (0.1) |
| – Local | 13,610 (34.4) | 11,498 (29.1) | 440 (1.1) | 1404 (3.6) | 196 (0.5) |
| – Regional | 13,343 (33.8) | 11,123 (28.1) | 414 (1.0) | 1504 (3.8) | 220 (0.6) |
| – Distant | 7255 (18.4) | 5980 (15.1) | 284 (0.7) | 831 (2.1) | 118 (0.3) |
| – Unknown | 2576 (6.5) | 2161 (5.5) | 84 (0.2) | 291 (0.7) | 28 (0.1) |

[†]Due to rounding, percentages may not add to 100%.

**Table 2. Age-adjusted annual incidence trends, Colorado Central Cancer Registry: colorectal cases (1992–2002).**

| Category | Total (%) | 0–49 (%) | ≥50 (%) |
|---|---|---|---|
| Total | -0.7 | -0.1 | -0.7 |
| Race/ethnicity: | | | |
| – Caucasian | -0.7 | -0.2 | -0.8 |
| – Hispanic | +0.4 | +0.8 | -0.4 |
| – African–American | -4.4[*] | -0.3 | -4.7[*] |
| – Asian | -0.4 | -0.9 | -0.2 |
| Sex: | | | |
| – Male | -0.9 | -0.9 | -0.9 |
| – Female | -0.6 | +0.9 | -0.7 |
| Tumor stage at diagnosis: | | | |
| – Early stage | +1.3 | +0.9 | +2.3[*] |
| – Late stage | -2.4[*] | -0.8 | -2.6[*] |
| Anatomical location: | | | |
| – Left-sided | -1.1[*] | +0.4 | -1.3[*] |
| – Right-sided | -0.5 | -1.3 | -0.5 |

[*]$p < 0.05$

Table 3. Age-adjusted annual incidence trends, Colorado Central Cancer Registry: colorectal cases (2003–2013).

| Category | Total (%) | 0–49 (%) | ≥50 (%) |
|---|---|---|---|
| Total | -3.8* | +1.7 | -4.3* |
| Race/ethnicity: | | | |
| – Caucasian | -3.7* | +2.5* | -4.3* |
| – Hispanic | -4.2* | -0.9 | -4.6* |
| – African–American | -2.8* | +0.9 | -3.2* |
| – Asian | -2.7 | -8.5 | -2.5 |
| Age at diagnosis: | | | |
| – Males | -4.0* | +2.7* | -4.7* |
| – Females | -3.7* | +0.6 | -4.0* |
| Tumor stage at diagnosis | | | |
| – Early stage | -4.0* | +0.8 | -4.4* |
| – Late stage | -3.3* | +2.4* | -4.1* |
| Anatomical location: | | | |
| – Left-sided | -3.8* | +2.1* | -4.6* |
| – Right-sided | -3.5* | +1.8 | -4.0* |

*$p < 0.05$

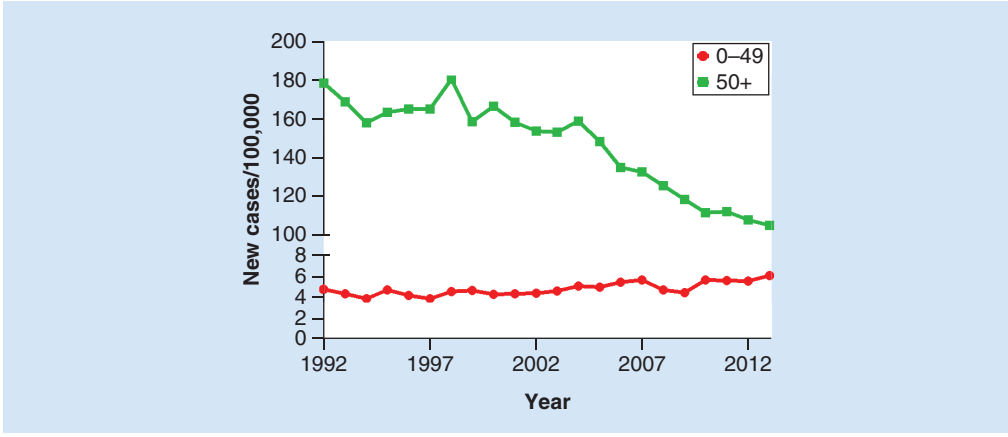


**Figure 1. Age-adjusted incidence (new cases/100,000 persons/year) of colorectal cancers in Colorado, stratified by 0–49 years of age and ≥50 years, from 1992 through 2013.**

persistently higher in 0–49 years of age compared with those ≥50 years of age, with a 5-year survival of 67.0% in the 0–49 cohort and 62.5% in the ≥50 cohort (Figure 3). Additionally, it is worth noting that 5-year survival continues to trend down at stage as diagnosis becomes more advanced, regardless of age. Additionally, while left- and right-sided CRC mirrors the overall trends seen in the 0–49 and ≥50 cohorts, there is not a notable difference in anatomical distribution based on subject age at CRC diagnosis.

## Discussion

Overall, the absolute incidence of CRC continues to fall in Colorado, reflecting national trends. Specifically, in patients over 50, age-adjusted incidence fell 4.3% annually from 2003 through 2013 ($p < 0.05$). However, age-adjusted incidence of late stage CRC in patients under 50 increased 1.7% annually and 2.7% in males under 50, indicating a potential shift in the at-risk population given modern screening and treatment techniques. Despite these findings, 5-year relative survival data show consistently higher survival rates among subjects under 50 which persists irrespective of tumor stage, suggesting that further research is needed to elucidate these differences. Interestingly, CRC incidence sometimes differs markedly from the demographic breakdown of Colorado overall, most notably in the Caucasian population which is overrepresented, and the Hispanic population which is underrepresented [15].

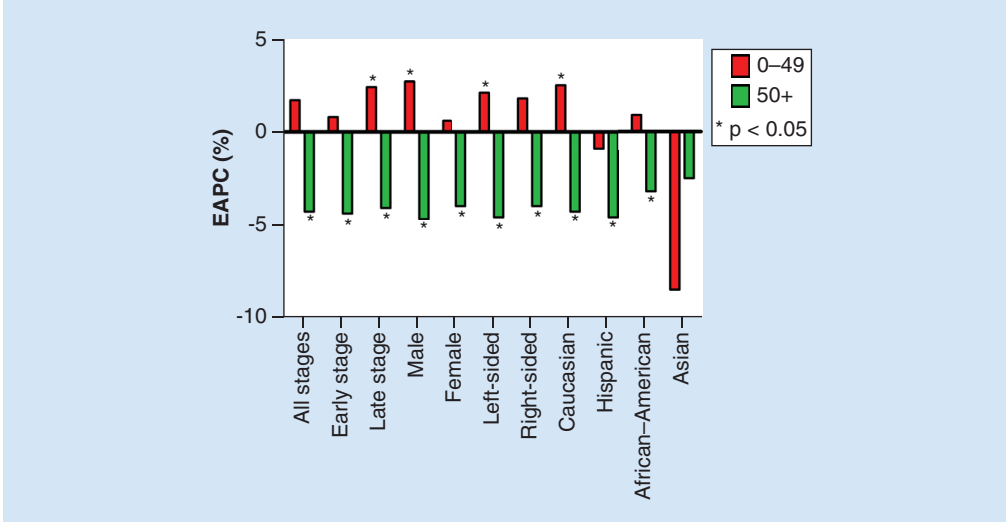


**Figure 2. Estimated annual percent change (EAPC %) of colorectal cancer incidence in Colorado, stratified by 0–49 years of age and ≥50 years, from 2003 through 2013.**

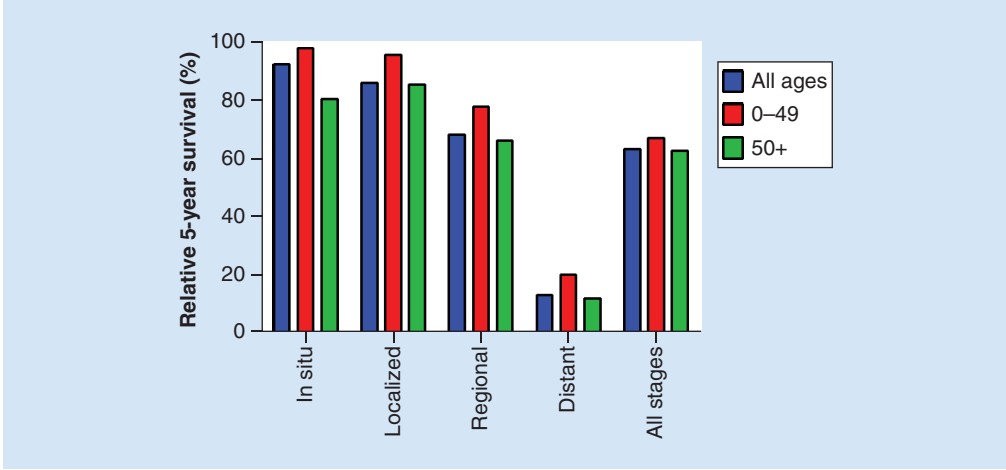


**Figure 3. Relative 5-year survival (%) of individuals with a colorectal cancer diagnosis compared with similar individuals without a diagnosis, stratified by 0–49 years of age and ≥50 years, from 2003 through 2009.**

The overall cause of rising incidence in YAs is still unknown, but there are multiple known risk factors that may be contributing to this trend, including genetic, environmental, or lifestyle-based. Indeed, the primary reason currently that adults in the prescreening age range (20–49 years) are assessed for CRCs is if there is a family history of hereditary CRC, such as familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer [17]. This is often compounded by demographic differences such as being uninsured [12] and CRC-related symptoms often being misattributed or ignored in this population [11], which would need to be accounted for if screening recommendations for YAs were implemented. There is emerging evidence that screening may not account for all of the decrease in CRC incidence [18], although it is unclear what role increased awareness and earlier detection may play, or if the trend may be driven by underlying dietary and lifestyle changes [13]. Additionally, recent research has shown a higher prevalence of germline cancer susceptibility mutations in patients with YA CRC, and a full third of those mutation-positive patients did not meet testing criteria for the gene(s) in which they had a mutation [19]. While recent guidelines by the US Preventive Services Task Force [6] and National Comprehensive Cancer Network [7] do not yet recommend screening earlier than age 50 for individuals of average risk, these genetic and epidemiologic findings point to a changing CRC population that is younger and more genomically unstable.

It should be noted that a weakness of this analysis is the inability to control the family history of CRC, which is an important risk factor and clinical consideration for CRC. Family history is not an outcome that is collected by the CCCR, however the addition of testing results for hereditary syndromes such as microsatellite instability and hereditary nonpolyposis colorectal cancer is under consideration for inclusion in the CCCR. This may serve as an alternative method to approximate familial risk of CRC if adequately available, regardless the generalizability of analysis drawn from a population-based dataset such as the CCCR which is a robust strength of this study.

Looking broadly, Colorado has markedly lower incidence of CRC than is seen nationally in the USA, with an age-adjusted incidence rate of 33.4 cases per 10,000 persons/year in 2012 [3] compared with 42.4 per 100,000 reported in 2012 in the national SEER database [2]. Relative survival for CRC is comparable in Colorado to national trends, with overall rates of 63.1% in Colorado and 64.9% nationally [2,3]. This study strengthens and expands upon the findings of earlier research that illustrated rising incidence of YA CRC in California [12] while offering a slightly different picture than is seen nationally [13], demonstrating the unique characteristics of Colorado to help uncover driving forces behind these trends. This study then expands upon these trends by analyzing survival trends and anatomical tumor distribution across age groups, in order to explore the nuances between traditional CRC and YA CRC.

The analysis found that while overall CRC incidence continues to fall, CRC incidence in subjects under age 50 is rising 1.7% per year, and 2.7% annually in men under age 50. However, no difference in anatomical distribution was seen between younger and older subjects, contrasting with previous studies [13], and younger subjects continued to have better 5-year survival than older subjects of similar tumor stages. Because of this persistent survival advantage despite a trend toward later stage tumors in the under 50 population, further analysis is warranted into potential biologic difference between tumors in younger and older patients. Additionally, differences in side-effect profiles and treatment strategies in younger and older patients would be particularly helpful in determining differences between YA CRC and CRC in older adults, as this may yield novel biologic insights, improve clinical options for patients with CRC and better define optimal CRC screening guidelines.

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No writing assistance was utilized in the production of this manuscript.

### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.



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