# Shifts in the Proportion of Distant Stage Early-Onset Colorectal Adenocarcinoma in the United States

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## ABSTRACT

**Background:** Carcinoids, frequently classified as "colorectal cancer" contribute to rising early-onset colorectal cancer (EOCRC) incidence rates (IR) and have distinct staging distributions compared to often advanced stage adenocarcinomas (screening target). Thus, assessing temporal shifts in early-onset distant stage adenocarcinoma can impact public health.

**Methods:** 2000–2016 Surveillance Epidemiology and End Results (SEER) 18 yearly adenocarcinoma IRs were stratified by stage (*in situ*, localized, regional, distant), age (20–29, 30–39, 40–49, 50–54-year-olds), subsite (colorectal, rectal-only, colon-only), and race [non-Hispanic whites, non-Hispanic Blacks (NHB), Hispanics] in 103,975 patients. Three-year average annual IR changes (pooled 2000–2002 IRs compared with 2014–2016) and cancer stage proportions (percent contribution of each cancer stage) were calculated.

**Results:** Comparing 2000–2002 with 2014–2016, the steepest percent increases are in distant stage cancers. Colon-only, distant adenocarcinoma increased most in 30–39-year-olds (49%, 0.75/100,000→1.12/100,00, $P < 0.05$). Rectal-only, distant stage increases were steepest in 20–29-year-olds (133%, 0.06/100,000→0.14/100,000, $P < 0.05$), followed by 30–39-year-olds (97%, 0.39/100,000→0.77/100,000, $P < 0.05$) and 40–49-year-olds (48%, 1.38/100,000→2.04/100,000, $P < 0.05$). Distant stage proportions (2000–2002 to 2014–2016) increased for colon-only and rectal-only subsites in young patients with the largest increases for rectal-only in 20–29-year-olds (18%→31%) and 30–39-year-olds (20%→29%). By race, distant stage proportion increases were largest for rectal-only in 20–29-year-old NHBs (0%→46%) and Hispanics (28%→41%). Distant colon proportion increased most in 20–29-year-old NHBs (20%→34%).

**Conclusions:** Youngest patients show greatest burdens of distant colorectal adenocarcinoma. Although affecting all races, burdens are higher in NHB and Hispanic subgroups, although case counts remain relatively low.

**Impact:** Optimizing earlier screening initiatives and risk-stratifying younger patients by symptoms and family history are critical to counteract rising distant stage disease.

## Introduction

Recent studies have demonstrated rising early-onset colorectal cancer (EOCRC) incidence rates (IR) in the United States (1–3). Furthermore, studies have shown increases in distant stage disease in young patients. For example, the average annual percent change (APC) for distant stage colorectal cancer in 40–49-year-olds was 2.9% in a Surveillance Epidemiology and End Results (SEER) 9 study population from 1995–2015 (4). In another study, a nonsignificant APC increase (0.43%) in the incidence of distant stage colon cancer was seen in 35–49-year-olds from 1975–2010; however, a significant increase (1.81%) in APC was seen in colonic distant stage disease in 20–34-year-olds. For distant stage rectal cancer, there was a significant APC in both 20–34-year-olds and 35–49-year-olds of 2.66% and 1.46%, respectively (5).

Two questions emerge from review of these studies. The first is how proportions of distant stage disease (i.e., presence of metastasis) are shifting within age groups and subsites over time. Prior EOCRC staging studies have utilized APC analysis, which provides a modeled trend of incidence over time for a given cancer stage (6). Because APCs are fitted trends, they cannot be compared among one another to generate cancer stage proportions. They can only indicate whether a trend is increasing/decreasing. Furthermore, a very high APC value may correspond to a very low change in absolute IRs and thus the overall contribution (i.e., proportion) of a given cancer stage may be minimal. Hence, instead of relying on APC analyses, focusing on shifts in the proportion of cancer stage is critical and can have important public health implications (7). For example, for those in their 40's, cancer stage proportion analysis is important given recent controversy over whether average risk screening should begin at age 45 or 50. In 2021, the U.S. Preventive Services Task Force (USPSTF) endorsed average-risk screening initiation at age 45 (8). However, colorectal cancer screening rates in younger patients (i.e., those in their 50's) have historically been suboptimal (9). Hence an assessment of distant stage colorectal cancer burden in younger patients has the potential to motivate population-based screening and optimize real-world screening rates.

The second question relates to adenocarcinoma histologic subtypes. SEER registries include all histologic subtypes, including carcinoids (neuroendocrine tumors), under the category of "colorectal cancer." Prior studies have not reported histologic subgroup analyses. However, because adenocarcinomas are the target of screening and diagnostic testing (as opposed to other subtypes like carcinoids), an understanding of adenocarcinoma staging is critical. In addition, carcinoids have been increasing in younger patients, potentially

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impacting overall colorectal cancer incidence and stage reporting (10). Despite sometimes being perceived as rare, colorectal carcinoids are common, particularly rectal carcinoids. Prior analyses have revealed up to 34%, 20%, 14%, and 23% of rectal cancers are carcinoids in 20–29, 30–39, 40–49, and 50–54-year-olds, respectively. These tumors are much more likely to present with early-stage disease compared with rectal adenocarcinomas, thus highlighting the importance of analyzing adenocarcinoma staging independently from carcinoids (11).

In this context, we utilized SEER 18 data stratified by age (20–29, 30–39, 40–49, and 50–54-year-olds), subsite (colon versus rectal), race/ethnicity (non-Hispanic whites, non-Hispanic Blacks and Hispanics) and stage (*in situ*, localized, regional, and distant) to determine how proportions of cancer stage are shifting over time from 2000 to 2016. Furthermore, we used pooled IRs from 2000–2016 to determine which age subgroups have the highest proportion of distant stage disease. Finally, in contrast to prior studies in which histologic subtypes of colorectal cancer were not reported, we focused specifically on adenocarcinomas.

## Materials and Methods

Age-adjusted IRs of SEER 18 colorectal cancer cases (adenocarcinoma histologic subtype) from 2000–2016 were acquired using SEER*Stat (version 8.3.6; NCI; see Supplementary Materials and Methods) and adjusted to the year 2000 U.S. population (12). The SEER 18 registries were chosen given their high-quality datasets and inclusion of more urban and diverse patient populations compared with other registries (12). Cancer stage (*in situ*, localized, regional, and distant) analysis was conducted and stratified by age group (20–29, 30–39, 40–49, and 50–54-year-olds) and anatomic subsite (colon-only, rectal-only, and combined colorectal). Although 50–54-year-olds do not necessarily fall under the definition of EOCRC, data were collected because of increasing colorectal cancer incidence in this group (3). For anatomic subsites, the appendix was excluded because of appendiceal cancers potentially creating biases in colon-only IR and stage reporting (13). Because unknown stage cases will impact staging shifts, unknown stage cases were included into the proportional analyses. Including unknown cases is the standard methodology to accurately determine staging shifts (unknown cases are included into the overall case count denominator when calculating an incidence proportion). A subanalysis of unknown stage adenocarcinomas was performed to ensure unknown cases did not significantly impact results (Supplementary Table S1).

Colorectal cancer IRs for each individual calendar year (2000–2016) and the contribution (proportion) of each cancer stage to the overall IR for each subgroup (age and subsite) were calculated. Further analysis was performed in which 3-year average annual IRs were assessed from the beginning of the study period to the end. Pooled IRs from 2000–2002 and 2014–2016 were compared to assess for both percent changes in incidence rates and shifts in cancer stage proportions over time. Assessing pooled IRs at the study flanks (2000–2002 and 2014–2016) allows one to compensate for variations of IRs that may occur in individual calendar years. There is precedent for this type of analysis given use in prior studies (3, 10). To obtain a 3-year average annual IR, an age group's case count over a 3-year period was divided by the corresponding age group's SEER 18 population over the same 3-year period and then corrected to a population count of 100,000. Rate ratios (3-year average annual comparisons between the different time periods) and associated confidence intervals (CI) were generated by SEER*Stat with the recommended Tiwari 95% CI option applied to determine significance. Rate ratios were considered significant if CIs did not cross 1 (Supplementary Table S2).

For each of the above analyses, subanalyses were stratified by race/ethnicity (non-Hispanic white, non-Hispanic Black, and Hispanic) to assess the impact that race/ethnicity may have on changes in IRs and staging proportions over time. Because of lower case counts, information on other races/ethnicities including American Indian/Alaskan Native and Asian or Pacific Islander were not included.

In addition, pooled IRs (all races/ethnicities combined), as opposed to changes over time, from 2000–2016 were also calculated and early-age subgroups were compared. This will allow determination of which subgroups (by age and subsite) have the highest proportion of distant stage disease.

## Results

Study participant characteristics are reported in **Table 1**. There were 103,975 patients representing 106,871 colorectal cancer cases (case counts were greater than patient counts due to the rare situation of patients presenting with synchronous colorectal cancers). The CONSORT diagram is reported in Supplementary Fig. S1.

### IRs stratified by age, subsite, and stage from 2000–2002 to 2014–2016 (percent change in cancer stages)

*In situ* adenocarcinomas are decreasing in most age groups and subsites when comparing 2000–2002 with 2014–2016 (**Table 2**). There is no consistent increase in localized adenocarcinomas in the various subgroups. Conversely, regional adenocarcinomas demonstrate statistically significant increases in most subgroups, particularly within the rectal subsite. For example, there is a statistically significant increase of 45% (0.80/1,000 to 1.16/100,000, $P < 0.05$), 43% (2.80/100,000 to 4.01/100,000, $P < 0.05$), and 24% (6.41/100 to 7.97/100,000, $P < 0.05$) for 30–39-year-olds, 40–49-year-olds, and 50–54-year-olds, respectively for regional stage rectal adenocarcinoma. However, the steepest increases are in distant stage disease. For the colon-only subsite, the steepest increase in distant stage disease was 49% (0.75/100,000 to 1.12/100,000, $P < 0.05$) in 30–39-year-olds. For the rectal subsite, the steepest increase was 133% in 20–29-year-olds (0.06/100,000 to 0.14/100,000, $P < 0.05$), followed by 30–39-year-olds

**Table 1.** SEER 18 demographic distribution of adenocarcinoma ages 20–54.

| | |
|---|---|
| Total patients after stratification | 103,975 |
| Ages | 20–54 years-old |
| Race | Number of patients (with % of total patients) |
| Non-Hispanic White | 63,756 (61.3%) |
| Black | 14,792 (14.2%) |
| Hispanic | 14,946 (13.9%) |
| Asian/Pacific Islander | 9,248 (8.9%) |
| Native American/Alaskan Native | 902 (0.9%) |
| Unknown race | 781 (0.8%) |
| Sex | |
| Female | 47,393 (46.0%) |
| Male | 56,582 (54.0%) |
| Stage | |
| *In situ* | 5,154 (5.0%) |
| Localized | 34,420 (33.0%) |
| Regional | 40,346 (38.8%) |
| Distant | 24,055 (23.1%) |

**Table 2.** SEER 18 3-year average annual adenocarcinoma incidence rate comparisons from 2000–2002 to 2014–2016 for *in situ*, localized, regional, and distant stages.

| 3-Year average annual adenocarcinoma *in situ* incidence 2000–2002 vs. 2014–2016 | | | | |
|---|---|---|---|---|
| **Site** | **Age** | **2000–2002** | **2014–2016** | **Absolute change (% change)** |
| Colorectal | 20–29 | 0.03/100,000 (CI 0.01↔0.06) | 0.03/100,000 (CI 0.02↔0.06) | +0.00 (↑0%) |
| | 30–39 | 0.23/100,000 (CI 0.19↔0.29) | 0.15/100,000 (CI 0.11↔0.19) | −0.08 (↓35%)[a] |
| | 40–49 | 1.16/100,000 (CI 1.05↔1.28) | 0.53/100,000 (CI 0.46↔0.61) | −0.63 (↓54%)[a] |
| | 50–54 | 4.32/100,000 (CI 4.00↔4.67) | 2.47/100,000 (CI 2.25↔2.70) | −1.85 (↓43%)[a] |
| Colon-only | 20–29 | 0.02/100,000 (CI 0.01↔0.04) | 0.01/100,000 (CI 0.00↔0.03) | −0.01 (↓50%) |
| | 30–39 | 0.15/100,000 (CI 0.11↔0.20) | 0.10/100,000 (CI 0.07↔0.14) | −0.05 (↓33%) |
| | 40–49 | 0.69/100,000 (CI 0.61↔0.79) | 0.36/100,000 (CI 0.30↔0.42) | −0.36 (↓48%)[a] |
| | 50–54 | 3.06/100,000 (CI 2.79↔3.35) | 1.75/100,000 (CI 1.56↔1.95) | −1.31 (↓43%)[a] |
| Rectal-only | 20–29 | 0.01/100,000 (CI 0.00↔0.03) | 0.02/100,000 (CI 0.01↔0.04) | +0.01 (↑100%) |
| | 30–39 | 0.08/100,000 (CI 0.06↔0.12) | 0.05/100,000 (CI 0.03↔0.08) | −0.03 (↓38%) |
| | 40–49 | 0.47/100,000 (CI 0.40↔0.54) | 0.17/100,000 (CI 0.13↔0.22) | −0.30 (↓64%)[a] |
| | 50–54 | 1.26/100,000 (CI 1.09↔1.45) | 0.72/100,000 (CI 0.60↔0.85) | −0.54 (↓43%)[a] |
| **3-Year average annual adenocarcinoma localized incidence 2000–2002 vs. 2014–2016** | | | | |
| **Site** | **Age** | **2000–2002** | **2014–2016** | **Absolute change (% change)** |
| Colorectal | 20–29 | 0.24/100,000 (CI 0.19↔0.29) | 0.26/100,000 (CI 0.21↔0.31) | +0.02 (↑8%) |
| | 30–39 | 1.44/100,000 (CI 1.32↔1.57) | 1.60/100,000 (CI 1.47↔1.74) | +0.16 (↑11%) |
| | 40–49 | 6.07/100,000 (CI 5.82↔6.33) | 6.12/100,000 (CI 5.86↔6.38) | +0.05 (↑1%) |
| | 50–54 | 18.46/100,000 (CI 17.79↔19.16) | 20.47/100,000 (CI 19.82↔21.13) | +2.01 (↑11%)[a] |
| Colon-only | 20–29 | 0.13/100,000 (CI 0.10↔0.18) | 0.18/100,000 (CI 0.14↔0.22) | +0.05 (↑38%) |
| | 30–39 | 0.87/100,000 (CI 0.78↔0.97) | 1.00/100,000 (CI 0.90↔1.11) | +0.13 (↑15%) |
| | 40–49 | 3.52/100,000 (CI 3.33↔3.71) | 3.81/100,000 (CI 3.61↔4.02) | +0.29 (↑8%)[a] |
| | 50–54 | 11.41/100,000 (CI 10.88↔11.96) | 13.56/100,000 (CI 13.04↔14.11) | +1.15 (↑19%)[a] |
| Rectal-only | 20–29 | 0.10/100,000 (CI 0.07↔0.15) | 0.08/100,000 (CI 0.06↔0.12) | −0.02 (↓20%) |
| | 30–39 | 0.57/100,000 (CI 0.50↔0.66) | 0.59/100,000 (CI 0.52↔0.68) | +0.02 (↑4%) |
| | 40–49 | 2.56/100,000 (CI 2.39↔2.72) | 2.31/100,000 (CI 2.16↔2.47) | −0.25 (↓10%)[a] |
| | 50–54 | 7.05/100,000 (CI 6.64↔7.49) | 6.91/100,000 (CI 6.53↔7.30) | −0.14 (↓2%) |
| **3-Year average annual adenocarcinoma regional incidence 2000–2002 vs. 2014–2016** | | | | |
| **Site** | **Age** | **2000–2002** | **2014–2016** | **Absolute change (% change)** |
| Colorectal | 20–29 | 0.47/100,000 (CI 0.40↔0.55) | 0.55/100,000 (CI 0.48↔0.63) | +0.08 (↑17%) |
| | 30–39 | 2.25/100,000 (CI 2.10↔2.41) | 2.82/100,000 (CI 2.64↔3.00) | +0.57 (↑25%)[a] |
| | 40–49 | 7.62/100,000 (CI 7.34↔7.91) | 9.39/100,000 (CI 9.07↔9.71) | +1.77 (↑23%)[a] |
| | 50–54 | 18.40/100,000 (CI 17.73↔19.10) | 19.02/100,000 (CI 18.40↔19.66) | +0.22 (↑3%) |
| Colon-only | 20–29 | 0.33/100,000 (CI 0.27↔0.40) | 0.36/100,000 (CI 0.30↔0.42) | +0.03 (↑9%) |
| | 30–39 | 1.45/100,000 (CI 1.33↔1.58) | 1.66/100,000 (CI 1.52↔1.80) | +0.21 (↑14%)[a] |
| | 40–49 | 4.82/100,000 (CI 4.60↔5.05) | 5.38/100,000 (CI 5.14↔5.62) | +0.56 (↑12%)[a] |
| | 50–54 | 11.99/100,000 (CI 11.45↔12.55) | 11.05/100,000 (CI 10.58↔11.54) | −0.94 (↓8%)[a] |
| Rectal-only | 20–29 | 0.14/100,000 (CI 0.10↔0.19) | 0.19/100,000 (CI 0.15↔0.24) | +0.05 (↑36%) |
| | 30–39 | 0.80/100,000 (CI 0.71↔0.90) | 1.16/100,000 (CI 1.05↔1.28) | +0.36 (↑45%)[a] |
| | 40–49 | 2.80/100,000 (CI 2.63↔2.98) | 4.01/100,000 (CI 3.81↔4.23) | +1.21 (↑43%)[a] |
| | 50–54 | 6.41/100,000 (CI 6.02↔6.83) | 7.97/100,000 (CI 7.57↔8.39) | +1.56 (↑24%)[a] |
| **3-Year average annual adenocarcinoma distant incidence 2000–2002 vs. 2014–2016** | | | | |
| **Site** | **Age** | **2000–2002** | **2014–2016** | **Absolute change (% change)** |
| Colorectal | 20–29 | 0.21/100,000 (CI 0.17↔0.27) | 0.33/100,000 (CI 0.27↔0.39) | +0.12 (↑57%)[a] |
| | 30–39 | 1.14/100,000 (CI 1.04↔1.26) | 1.89/100,000 (CI 1.75↔2.04) | +0.75 (↑66%)[a] |
| | 40–49 | 4.33/100,000 (CI 4.12↔4.55) | 6.12/100,000 (CI 5.86↔6.38) | +1.79 (↑41%)[a] |
| | 50–54 | 9.56/100,000 (CI 9.08↔10.07) | 10.97/100,000 (CI 10.50↔11.46) | +1.41 (↑15%)[a] |
| Colon-only | 20–29 | 0.16/100,000 (CI 0.12↔0.20) | 0.19/100,000 (CI 0.14↔0.20) | +0.03 (↑19%) |
| | 30–39 | 0.75/100,000 (CI 0.67↔0.85) | 1.12/100,000 (CI 1.01↔1.24) | +0.37 (↑49%)[a] |
| | 40–49 | 2.94/100,000 (CI 2.77↔3.12) | 4.07/100,000 (CI 3.87↔4.29) | +1.13 (↑38%)[a] |
| | 50–54 | 6.81/100,000 (CI 6.40↔7.24) | 7.32/100,000 (CI 6.94↔7.72) | +0.51 (↑7%) |
| Rectal-only | 20–29 | 0.06/100,000 (CI 0.04↔0.09) | 0.14/100,000 (CI 0.11↔0.19) | +0.08 (↑133%)[a] |
| | 30–39 | 0.39/100,000 (CI 0.33↔0.46) | 0.77/100,000 (CI 0.68↔0.87) | +0.38 (↑97%)[a] |
| | 40–49 | 1.38/100,000 (CI 1.27↔1.51) | 2.04/100,000 (CI 1.90↔2.20) | +0.66 (↑48%)[a] |
| | 54–54 | 2.75/100,000 (CI 2.49↔3.03) | 3.65/100,000 (CI 3.38↔3.93) | +0.90 (↑33%)[a] |

[a]2014–2016 value significantly changed from 2000–2002 value to $P < 0.05$. Relative percent change of 2000–2002 IR to 2014–2016 IR are provided in parentheses in rightmost column.

**Table 3.** SEER 18 adenocarcinoma staging contribution (proportion) shifts between 2000–2002 and 2014–2016 (all races combined).

| Staging percent contribution (proportions) of overall adenocarcinoma between 2000–2002 vs. 2014–2016 (all races combined) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *In situ* | | | *Localized* | | | *Regional* | | | Distant | | |
| *Subsite/age* | | 2000–2002 | 2014–2016 | Δ | 2000–2002 | 2014–2016 | Δ | 2000–2002 | 2014–2016 | Δ | 2000–2002 | 2014–2016 | Δ |
| Colorectal | 20–29 | 3% | 2% | −1 | 24% | 21% | −3 | 48% | 45% | −3 | 21% | 27% | +6 |
| | 30–39 | 4% | 2% | −2 | 29% | 24% | −5 | 43% | 43% | +0 | 22% | 29% | +7 |
| | 40–49 | 6% | 2% | −4 | 31% | 27% | −4 | 39% | 42% | +3 | 22% | 27% | +5 |
| | 50–54 | 8% | 5% | −3 | 36% | 38% | +2 | 35% | 35% | +0 | 18% | 20% | +2 |
| Colon-only | 20–29 | 3% | 1% | −2 | 20% | 24% | +4 | 51% | 47% | −4 | 25% | 25% | +0 |
| | 30–39 | 5% | 3% | −2 | 26% | 25% | −1 | 44% | 42% | −2 | 23% | 28% | +5 |
| | 40–49 | 6% | 3% | −3 | 29% | 27% | −2 | 39% | 39% | +0 | 24% | 29% | +5 |
| | 50–54 | 9% | 5% | −4 | 34% | 40% | +6 | 35% | 32% | −3 | 20% | 21% | +1 |
| Rectal-only | 20–29 | 3% | 4% | +1 | 30% | 18% | −12 | 42% | 42% | +0 | 18% | 31% | +13 |
| | 30–39 | 4% | 2% | −2 | 30% | 22% | −8 | 42% | 44% | +2 | 20% | 29% | +9 |
| | 40–49 | 6% | 2% | −4 | 34% | 27% | −7 | 37% | 46% | +9 | 18% | 23% | +5 |
| | 50–54 | 7% | 4% | −3 | 39% | 35% | −4 | 35% | 40% | +5 | 15% | 18% | +3 |

Note: Staging shift analysis includes unknown stage cases to accurately calculate percent each stage's contribution to overall adenocarcinoma over the 3-year interval. Δ absolute value difference between 2000–2002 proportion value and 2014–2016 proportion value for each respective stage.

(97%, 0.39/100,000 to 0.77/100,000, $P < 0.05$) and 40–49-year-olds (48%, 1.38/100,000 to 2.04/100,000, $P < 0.05$).

### Shifts in the proportion of distant stage disease by study flanks (2000–2002 vs. 2014–2016) and individual calendar year

#### Distant stage disease

The proportion of distant stage disease from 2000–2002 to 2014–2016 increased for both colon and rectal cancer in almost all age groups (**Table 3**). The steepest increases in proportion for any stage of disease were in the distant category but were more pronounced for rectal subsites. For example, from 2000–2002 to 2014–2016, the largest percent increases of distant stage proportions were for rectal adenocarcinoma in 20–29-year-olds (18%→31%) and 30–39-year-olds (20%→29%).

When individual calendar years are analyzed, similar trends were found (**Fig. 1**). Distant stage adenocarcinomas in 30–39-year-olds, 40–49-year-olds, and 50–54-year-olds make up an increasing proportion of overall colorectal cancer stage with progressive calendar years (**Fig. 1**). This trend is most pronounced for colon adenocarcinoma in 30–39 and 40–49-year-olds and rectal adenocarcinoma in 30–39 and 40–49-year-olds (Supplementary Fig. S2).

#### Regional stage disease

From 2000–2002 to 2014–2016, the proportion of regional stage disease remained similar in most age groups and subsites (**Table 3**). However, there was a relatively steep increase in the proportion of regional stage disease for rectal adenocarcinoma in 40–49-year-olds (37%→46%).

When individual calendar years are analyzed, similar trends are observed (**Fig. 1**). The most consistently increasing regional stage proportion was in the 40–49 and 50–54-year-old rectal adenocarcinoma subgroups (Supplementary Fig. S2).

#### *In situ* and localized stage disease

The proportion of *in situ* and localized stage disease decreased for most subsites and age groups from 2000–2002 to 2014–2016 (**Table 3**). The most pronounced decrease in proportions were for localized rectal adenocarcinomas in 20–29-year-olds (30%→18%), 30–39-year-olds (30%→22%), and 40–49-year-olds (34%→27%).

When individual calendar years were analyzed, similar trends were demonstrated (**Fig. 1**). Localized rectal adenocarcinomas in 20–29, 30–39, 40–49, and 50–54-year-olds steadily decreased and were more pronounced than other subgroups (Supplementary Fig. S2).

### Pooled IRs over 2000–2016 stratified by age group, subsite, and stage

There is a direct correlation between decreasing age and the relative likelihood of presenting with distant or regional stage disease (**Fig. 2**). For combined site colorectal adenocarcinoma, 20% of 50–54-year-olds present with distant stage disease compared with 25% in 40–49-year-olds, 27% in 30–39-year-olds, and 29% in 20–29-year-olds. This trend is most prominent for the rectal subsite. Conversely, for combined site colorectal adenocarcinoma, 38% of 50–54-year-olds present with localized disease, compared with 30% in 40–49-year-olds, 26% in 30–39-year-olds, and 24% in 20–29-year-olds.

### Shifts in distant stage proportions by race/ethnicity

Three-year average IR changes from 2000–2002 to 2014–2016 for each race/ethnicity are provided in Supplementary Tables S3–S8. **Table 4** summarizes these findings and as can be seen, the proportion of distant stage colorectal adenocarcinoma increased from 2000–2002 to 2014–2016 in non-Hispanic White patients in all age groups and subsites except for the 20–29-year-old colon-only subgroup. The increase in proportion of distant stage colorectal adenocarcinoma was most notable in 30–39 and 40–49-year-olds (21%→29% and 20%→27%, respectively). Among all racial subgroups, the largest increases in distant stage proportion were observed at the rectal subsite in non-Hispanic Blacks in 20–29-year-olds (0%→46%), colon subsite in non-Hispanic Blacks in 20–29-year-olds (20%→34%), rectal subsite in Hispanics in 20–29-year-olds (28%→41%) and rectal subsite in non-Hispanic Blacks in 30–39-year-olds (21%→33%). However, case counts in these subgroups were relatively low compared with older patients.

## Discussion

This is, to our knowledge, the first study to assess EOCRC staging IR proportions with a focus on adenocarcinomas. Several trends were uncovered. First, distant stage proportions are increasing over time in most early-onset subgroups with a corresponding decrease in early-stage disease. Second, there is a direct correlation between younger age and the higher relative likelihood of presenting with distant stage disease. Finally, although the increasing burden of distant stage disease

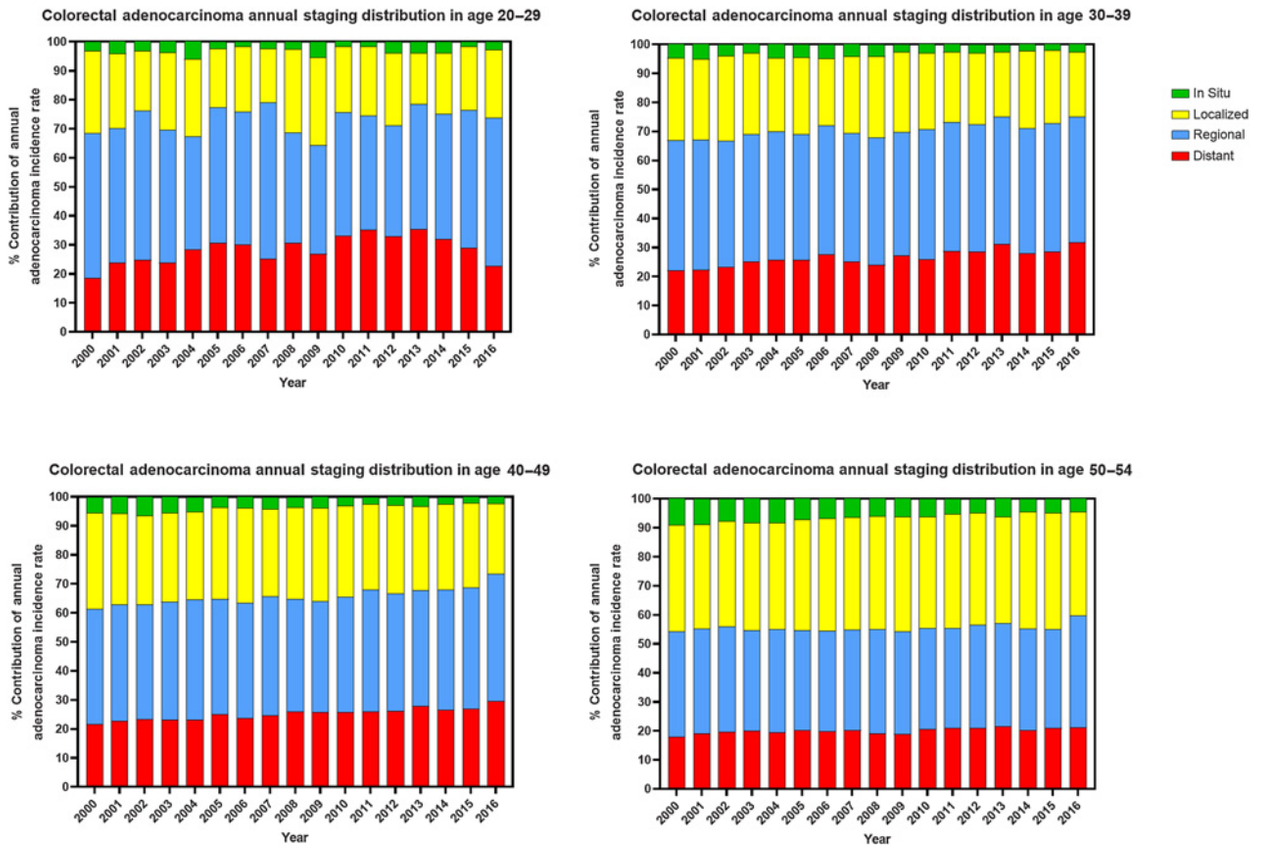


**Figure 1.**

SEER 18 individual stage percent contributions to overall colorectal annual adenocarcinoma from 2000–2016. Combined colorectal for age 20–29 (top left), age 30–39 (top right), age 40–49 (bottom left), and 50–54 (bottom right) are displayed individually. Within each year, colored bars are stacked to total 100% of adenocarcinomas.

is affecting all races, these changes are most notable in the youngest non-Hispanic black and Hispanic subgroups although absolute case counts remain relatively low in these younger patients.

With regard to staging proportions, cases of distant stage disease are contributing increasingly to the overall rectal and colon cancer burden over time for both the rectal and colon subsites and in all age groups. However, the most prominent contributions are for the rectal subsite in 20–29-year-olds and 30–39-year-olds. These results correlate with our assessment of distant stage percent increases over time in which IRs from 2000–2002 were compared with 2014–2016.

Although there is an increasing burden of distant stage disease in younger patients, absolute IRs in the youngest subgroups are relatively low. For example, in 20–29-year-olds, there was a statistically significant increase of 133% for distant stage rectal adenocarcinoma;

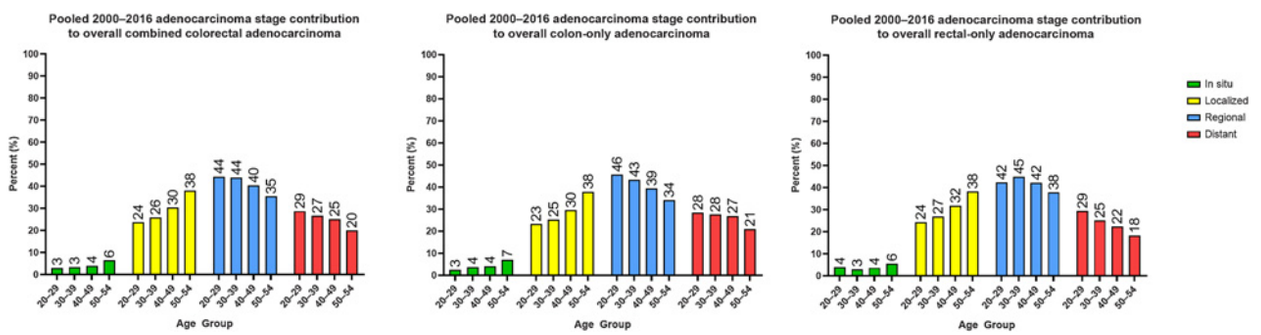


**Figure 2.**

SEER 18 pooled 2000–2016 adenocarcinoma stage contributions by age and subsite. Numbers above each bar represent percent contribution of each stage to pooled 2000–2016 overall adenocarcinoma incidence.

**Table 4.** SEER 18 adenocarcinoma staging proportion shifts between 2000–2002 and 2014–2016 stratified by race/ethnicity.

**Adenocarcinoma proportion shifts: *Distant stage***

| | | *Non-Hispanic White* | | | *Non-Hispanic Black* | | | *Hispanic* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Subsite/age*** | | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ |
| Colorectal | 20–29 | 23% | 25% | +2 | 13% | 38% | +25 | 25% | 30% | +5 |
| | 30–39 | 21% | 29% | +8 | 22% | 29% | +7 | 25% | 27% | +2 |
| | 40–49 | 20% | 27% | +7 | 31% | 29% | −2 | 24% | 27% | +3 |
| | 50–54 | 18% | 20% | +2 | 21% | 25% | +4 | 22% | 20% | −2 |
| Colon-only | 20–29 | 26% | 26% | +0 | 20% | 34% | +14 | 22% | 22% | +0 |
| | 30–39 | 23% | 30% | +7 | 23% | 27% | +4 | 22% | 25% | +3 |
| | 40–49 | 22% | 30% | +8 | 33% | 31% | −2 | 25% | 28% | +3 |
| | 50–54 | 20% | 22% | +2 | 22% | 25% | +3 | 23% | 21% | −2 |
| Rectal-only | 20–29 | 17% | 23% | +7 | 0% | 46% | +46 | 28% | 41% | +13 |
| | 30–39 | 18% | 27% | +9 | 21% | 33% | +12 | 29% | 29% | +0 |
| | 40–49 | 16% | 23% | +7 | 27% | 24% | −3 | 20% | 26% | +6 |
| | 50–54 | 14% | 17% | +3 | 18% | 26% | +8 | 19% | 20% | +1 |

**Adenocarcinoma proportion shifts: *Regional stage***

| | | *Non-Hispanic White* | | | *Non-Hispanic Black* | | | *Hispanic* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Subsite/age*** | | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ |
| Colorectal | 20–29 | 48% | 48% | +0 | 47% | 38% | −9 | 47% | 43% | −4 |
| | 30–39 | 42% | 41% | −1 | 43% | 45% | +2 | 44% | 45% | +1 |
| | 40–49 | 39% | 41% | +2 | 35% | 41% | +6 | 37% | 42% | +5 |
| | 50–54 | 35% | 36% | +1 | 37% | 31% | −6 | 37% | 35% | −2 |
| Colon-only | 20–29 | 49% | 47% | −2 | 48% | 45% | −3 | 52% | 47% | −5 |
| | 30–39 | 42% | 39% | −3 | 46% | 46% | +0 | 46% | 45% | −1 |
| | 40–49 | 40% | 39% | −1 | 35% | 38% | +3 | 39% | 38% | −1 |
| | 50–54 | 34% | 32% | −2 | 37% | 30% | −7 | 37% | 33% | −4 |
| Rectal-only | 20–29 | 46% | 49% | +3 | 41% | 31% | −10 | 38% | 36% | −2 |
| | 30–39 | 42% | 44% | +2 | 35% | 44% | +9 | 40% | 45% | +5 |
| | 40–49 | 38% | 44% | +6 | 36% | 50% | +14 | 34% | 48% | +14 |
| | 50–54 | 35% | 41% | +6 | 36% | 34% | −2 | 38% | 39% | +1 |

**Adenocarcinoma proportion shifts: *Localized Stage***

| | | *Non-Hispanic White* | | | *Non-Hispanic Black* | | | *Hispanic* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Subsite/age*** | | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ |
| Colorectal | 20–29 | 21% | 22% | +1 | 38% | 13% | −25 | 25% | 22% | −3 |
| | 30–39 | 29% | 25% | −4 | 28% | 20% | −8 | 25% | 24% | −1 |
| | 40–49 | 32% | 28% | −4 | 25% | 26% | +1 | 31% | 26% | −5 |
| | 50–54 | 37% | 38% | +1 | 31% | 37% | +6 | 33% | 36% | +3 |
| Colon-only | 20–29 | 19% | 24% | +5 | 31% | 15% | −16 | 19% | 25% | +6 |
| | 30–39 | 28% | 26% | −2 | 25% | 22% | −3 | 24% | 26% | +2 |
| | 40–49 | 30% | 27% | −3 | 24% | 28% | +4 | 28% | 29% | +1 |
| | 50–54 | 35% | 39% | +4 | 30% | 39% | +9 | 31% | 39% | +8 |
| Rectal-only | 20–29 | 26% | 19% | −7 | 52% | 10% | −42 | 34% | 16% | −18 |
| | 30–39 | 31% | 24% | −7 | 36% | 16% | −20 | 26% | 20% | −6 |
| | 40–49 | 36% | 28% | −8 | 26% | 21% | −5 | 36% | 21% | −15 |
| | 50–54 | 40% | 36% | −4 | 36% | 32% | −4 | 36% | 32% | −4 |

**Adenocarcinoma proportion shifts: *In situ stage***

| | | *Non-Hispanic White* | | | *Non-Hispanic Black* | | | *Hispanic* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Subsite/age*** | | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ | **2000–2002** | **2014–2016** | Δ |
| Colorectal | 20–29 | 4% | 3% | −1 | 0% | 6% | +6 | 2% | 1% | −1 |
| | 30–39 | 5% | 3% | −2 | 3% | 2% | −1 | 5% | 2% | −3 |
| | 40–49 | 6% | 2% | −4 | 6% | 2% | −4 | 5% | 2% | −3 |
| | 50–54 | 8% | 4% | −4 | 8% | 5% | −3 | 7% | 4% | −3 |
| Colon-only | 20–29 | 4% | 2% | −2 | 0% | 6% | +6 | 4% | 0% | −4 |
| | 30–39 | 5% | 3% | −2 | 4% | 3% | −1 | 6% | 2% | −4 |
| | 40–49 | 6% | 3% | −3 | 5% | 2% | -3 | 5% | 3% | −2 |
| | 50–54 | 9% | 5% | −4 | 9% | 5% | -4 | 9% | 5% | −4 |

*(Continued on the following page)*

**Table 4.** SEER 18 adenocarcinoma staging proportion shifts between 2000–2002 and 2014–2016 stratified by race/ethnicity. (Cont'd)

| Adenocarcinoma proportion shifts: *In situ stage* | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Non-Hispanic White* | | | *Non-Hispanic Black* | | | *Hispanic* | | |
| *Subsite/age* | | 2000–2002 | 2014–2016 | Δ | 2000–2002 | 2014–2016 | Δ | 2000–2002 | 2014–2016 | Δ |
| Rectal-only | 20–29 | 3% | 6% | +3 | 0% | 5% | +5 | 0% | 2% | +2 |
| | 30–39 | 6% | 2% | −4 | 1% | 0% | −1 | 3% | 2% | −1 |
| | 40–49 | 6% | 2% | −4 | 6% | 2% | −4 | 6% | 2% | −4 |
| | 50–54 | 7% | 4% | −3 | 6% | 5% | −1 | 5% | 3% | −2 |

Note: Staging shift analysis includes unknown stage cases to accurately calculate percent each stage's contribution to overall adenocarcinoma over the 3-year interval. Race/ethnic subgroup values are calculated from respective race/ethnicity denominators. Δ absolute value percent difference between 2000–2002 proportion value and 2014–2016 proportion value for each respective stage.

however, the corresponding IR rate increase was 0.06/100,000 to 0.14/100,000. In comparison, 50–54-year-olds demonstrated a 33% increase in distant stage rectal adenocarcinoma; however, the corresponding IRs were considerably higher: 2.75/100,000 over 2000–2002 to 3.65/100,000 over 2014–2016. These findings highlight the importance of conjointly assessing absolute IRs, as opposed to relying solely on percent changes, including APCs, to gauge public health impacts. In addition, when analyzing EOCRC staging trends, it is essential to couple IR shifts with a proportion analysis. If stage stratified IR changes are analyzed in isolation, this can be misleading as increases in a particular stage may be part of an overall increase in colorectal cancer incidence rates in general.

Understanding how the burden of distant stage disease in patients with EOCRC is changing over time is important because historically, patients under age 50 have not undergone preventative average-risk screening. The U.S. Preventive Services Task Force recently formalized the recommendation to initiate average-risk screening at age 45, instead of 50, in early 2021 (8). In 2008, the American College of Gastroenterology (ACG) recommended average-risk screening begin at age 45 in the African American population, but not other groups. Overall, the rise in distant stage disease burden prior to age 50 demonstrated in our study supports the potential benefits of earlier screening at age 45. In contrast to the 40–49-year-old Black population, the proportion of distant stage disease continues to increase in both the 40–49-year-old White and Hispanic populations, which further supports expanding average-risk screening to age 45 in all racial subgroups. A potential explanation for the decreased proportion of advanced stage disease in the 40–49-year-old Black population may be the ACG recommendation for earlier screening at age 45 in 2008. Furthermore, an important observation is that compared with other ages, the burden of distant stage disease in combined-race 50–54-years-olds has remained relatively stable (both in terms of percentage increase over time and shifts in distant stage proportions) compared with other ages. It is possible that screening initiation may blunt increases in distant stage disease by detecting cancers at an earlier stage or preventing cancer altogether through detection and removal of precancerous polyps.

It is important to note that patients under 45-years-old will not be eligible for average-risk screening. Hereditary colorectal cancer syndromes (i.e., Lynch syndrome and polyposis syndromes) are most likely to be diagnosed at younger ages, which stresses the importance of obtaining thorough family histories. In addition, there are often long delays between symptomatology onset and cancer diagnosis in young patients (14). As we have demonstrated, there is a direct correlation between decreasing age and presentation with distant stage disease, highlighting the risk to the youngest patients. The subgroups with the highest burden of distant stage disease were the youngest non-Hispanic Black and Hispanic patients. Although absolute case counts in these groups remain relatively low compared with older patients, particular attention needs to be placed on these patients going forward to help reverse this trend.

With regard to histologic subtype, it is important to note that approximately 15% of all EOCRCs are not adenocarcinomas. Adenocarcinomas, and not other histologic subtypes (i.e., carcinoids), are the focus of national screening initiatives. Inclusion of non-adenocarcinoma cancers in overall colorectal cancer staging analyses has the potential to significantly impact results. A prior histologic analysis of patients with EOCRC over 2000–2016 demonstrated that most colorectal carcinoids are identified in the rectum and that up to 34%, 20%, 14%, and 23% of rectal cancers are carcinoids in 20–29, 30–39, 40–49, and 50–54-year-olds, respectively (10). Within each age group, less than 5% of these rectal carcinoids were distant stage disease (11). In contrast, as we have revealed in our current analysis, in recent years, 18%–31% of rectal adenocarcinomas are distant stage disease, depending on age group. Given these disparate staging statistics, it is essential that carcinoids and adenocarcinomas not be pooled together during staging analyses. If carcinoids are included in colorectal cancer staging analyses, as in prior studies, this may lead to bias, particularly at the rectal subsite, in which cancers appear less aggressive than if adenocarcinomas are analyzed independently. It should be noted that colon carcinoids tend to be much more aggressive compared with rectal carcinoids. They are also much rarer, accounting for under 5% of all early-onset colon cancer histologic subtypes (10, 11).

Staging analysis must also take into consideration stage definitions established by the American Joint Committee on Cancer (AJCC; ref. 15). Over our study period, the AJCC has not changed the definition of what defines distant cancer (i.e., distant metastasis). The AJCC has developed more specific criteria within each individual stage, which has implications on metrics such as survival and prevalence. Given our study only focuses on incidence at initial diagnosis, our findings would not be impacted by these changes.

Study limitations include that due to the observational nature of our data, the etiology of increasing rates of distant stage disease in younger patients cannot be determined. Study strengths include utilization of the SEER 18 registry, which measures cancer IRs in approximately 28% of the U.S. population. Furthermore, compared to prior studies in which histologic subtype was not reported, we measured IRs for adenocarcinomas specifically, which are the target of screening and diagnostic testing. Finally, our analysis of cancer stage IR proportions provides novel information compared with prior studies which focused on APC calculations.

## Conclusion

Among patients with EOCRC, a heavy burden of distant stage colorectal cancer has become increasingly apparent. Distant stage

disease is making up a rising proportion of overall cancer stages in young patients of young patients and racial subgroups; however, this is particularly evident in the youngest non-Hispanic Black and Hispanic subgroups. Pooled IR rate analysis reveals a direct correlation between earlier age and development of distant stage disease; that is in a stepwise fashion, the younger the age, the higher relative likelihood to present with metastatic disease. Taken together, these results support the benefits of shifting the average-risk screening age from 50 to 45 for all patients and assuring that real-world screening rates are optimized. Furthermore, the results underscore that in patients younger than screening age, vigilant attention to concerning symptoms must be paid so that earlier diagnostic testing can be undertaken and that comprehensive family history assessments must take place so that earlier screening can be offered. Future studies are needed to understand why younger patients are increasingly likely to present with distant stage colorectal adenocarcinoma.

## Authors' Disclosures

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## Authors' Contributions

**E.M. Montminy:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **M. Zhou:** Data curation, formal analysis, methodology, writing–review and editing. **L. Maniscalco:** Data curation, validation, methodology, writing–review and editing. **R. Heda:** Formal analysis, validation, writing–review and editing. **M.K. Kim:** Formal analysis, validation, visualization, writing–review and editing. **S.G. Patel:** Formal analysis, validation, writing–review and editing. **X.-C. Wu:** Conceptualization, resources, data curation, formal analysis, validation, methodology, writing–review and editing. **S.H. Itzkowitz:** Conceptualization, formal analysis, validation, visualization, writing–original draft, writing–review and editing. **J.J. Karlitz:** Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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## Note

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

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