

Original Article

Sex and age-related differences in one-, three-, and five-year survival for early-onset colorectal cancer in Georgia

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Abstract: We examined the relationships of sex and age specific groups with cause-specific survival for early-onset colorectal cancer (EOCRC) diagnosis. A retrospective cohort analysis utilizing data from the 2000-2020 Georgia Cancer Registry were performed. Sex and age at diagnosis were exposures of interest. CRC survival at 1-, 3, and 5-year intervals were our primary outcomes of interest. Traditional Cox proportional hazards regression and Piecewise Cox regression models were performed to examine the mentioned association. Among 11,935 EOCRC patients, males had lower 1- (89.4% vs. 91.9%), 3- (75.7% vs. 79.2%), and 5-year (69.7% vs. 74.3%) survival rates than female patients (all p -value <0.001). In adjusted analysis, regardless of survival intervals, male patients aged 30-39 years were more likely to die from CRC at 1-year (HR, 1.40; 95% CI, 1.08-1.82), 3-year (HR, 1.26; 95% CI, 1.06-1.49), 5-year (HR, 1.27; 95% CI, 1.09-1.48) than female aged 30-39 years, respectively. Our piecewise models also confirmed male patients aged 30-39 years were 33% more likely to die from CRC within 1 year interval. Similarly, male patients aged 40-49 years were more likely to die from CRC at 1-year (HR, 1.33; 95% CI, 1.16-1.53), 3-year (HR, 1.20; 95% CI, 1.10-1.32), and 5-year (HR, 1.22; 95% CI, 1.13-1.33) intervals than female patients aged 40-49 years, respectively. In summary, the highest estimate of EOCRC mortality within 1-year interval was observed among male patients aged 30-39 years. Prioritizing prevention and treatment strategies may reduce the risk of 1-year EOCRC mortality for males and 30-39 age group.

Keywords: Sex, colorectal cancer, survival intervals, age at diagnosis, young adults

Introduction

Early-onset colorectal cancer (EOCRC) has been reported to be increasing most rapidly in adults younger than 50 years old in the United States (US) [1]. An increase in mortality of EOCRC was observed by approximately 1.3% per year from 2008 to 2017 with the exception for individuals aged 20-29 years [2]. However, there is a lack of evidence-based interventions that effectively reduce EOCRC mortality. This is concerning because younger populations are currently under the recommended screening age and may misdiagnose due to limited health-care access as a result of non-eligible for

screening [3]. This is especially true for Georgia, where a large proportion of medically underserved communities is associated with higher EOCRC mortality rates (2.0 vs. 1.8 per 100,000 in the US) [4].

While the factors driving EOCRC mortality remain unclear, they likely involve both individual-level characteristics (e.g., sex, race, lifestyle factors, personal/family history of CRC) and area-level factors (e.g., access to health care services) [5-17]. Notably, research highlights age and sex as critical determinants of outcomes. Males demonstrate consistently higher mortality rates globally and, in the U.S., particu-

larly in Southern US hotspots, with worse survival metrics than females [18-22]. Age-stratified analyses reveal distinct diagnostic patterns: advanced colon cancer predominates in patients aged 30-39 years versus advanced rectal cancer in those aged 20-29 years [23, 24]. Therefore, the research examines integrated relationship of sex and age-related difference is critical because it can inform the targeted interventions aimed at prioritizing prevention strategies for high-risk young populations.

However, there is insufficient comprehensive research exploring cause-specific survival of EOCRC at different time intervals while considering sex and age-related differences simultaneously. To address the research gaps, we sought to examine the relationship of sex and age-related disparities with cause-specific survival at 1-, 3-, and 5-year intervals for EOCRC in Georgia by adjusting for important covariates (e.g., geographic factors related to Georgia). We also examined sex differences in 1-, 3-, and 5-year survival rates within three ages at diagnosis groups (18-29, 30-39, and 40-49 years) using 2000-2020 Georgia Cancer Registry. Several Southeastern states, such as South Carolina, share similar socioeconomic and demographic profiles with Georgia - including lower median household income and higher proportions of Black populations [25]. This more regionally focused approach may have greater implications for other states and regions in the US, particularly in the Southeast.

Methods

Study design

We conducted a retrospective study integrating patient-level and county-level information from publicly available databases and de-identified cancer registries. Patient-level data from the 2000-2020 Georgia Cancer Registry were requested through Georgia Department of Public Health, which is a source for comprehensive population-based information in Georgia that includes patient demographics, primary tumor site, tumor morphology and stage at diagnosis, and follow-up for vital status. Further, we gathered patient residential socioeconomic status using data from the U.S. Department of Agriculture (USDA) Economic Research Service (ERS), <https://www.ers.usda>.

gov/. We linked USDA, ERS 2010 Rural-Urban Continuum (Beale) Code for rurality data and official ERS measure for persistent poverty data to patient-level data. The county Federal Information Processing System (FIPS) code was used as identifier to link Georgia Cancer Registry data (patient-level data) and geographic factors (county-level data) for CRC patients in Georgia. The study eligible population included patients diagnosed with CRC defined by the Surveillance, Epidemiology, and End Results (SEER) Site Recode ICD-O-3/WHO 2008 definition of colon cancer (C180-C189), rectosigmoid junction cancer (C199), and rectal cancer (C209). Data extracted for this study were approved by Institutional Review Boards (IRB) review at Georgia Department of Public Health, #240403.

Study participants

A total of 94,541 CRC patients were included between 2000 and 2020 in the Georgia Cancer Registry. We excluded 284 CRC patients aged under 18 years or with age unknown (n=108), missing information on race (n=112), missing survival time (n=1), CRC diagnosed before 2000 (n=27) and after 2021 (n=9), missing county code (n=8), unknown sex (n=6), and unknown primary site (n=13). The exclusion of cases diagnosed after 2021 due to limited sample size and because data beyond 2021 was not requested. To obtain an eligible study sample for EOCRC, we further excluded 82,322 patients who were diagnosed with CRC at the age of 50+ years. As a result, 11,935 patients aged 18-49 years diagnosed with CRC during 2000-2020 in Georgia were included as the study population for statistical analysis (**Figure 1**).

Measures

Sex (male or female at birth) and age at diagnosis (defined by around 10-year ranges within the definition of EOCRC, i.e., 18-29, 30-39, or 40-49 years) were exposures of interest. One-, three-, and five-year cause-specific survivals for CRC were our outcomes of interest. While the Five-year interval is a standard benchmark in cancer research, we also examined One- and Three-year survival intervals to highlight the urgency of EOCRC mortality among specific sex and age groups.

Sex and age related differences in EOCRC mortality

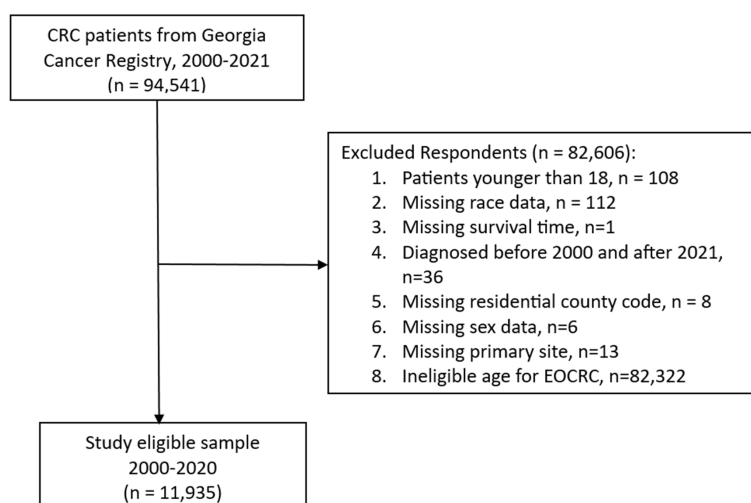


Figure 1. Study sample selection. Abbreviations: CRC, colorectal cancer; EO-CRC, early-onset colorectal cancer.

Covariates of interest include sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis. For sociodemographic characteristics, we included race [White, Black, Hispanic, Asian/Pacific Islander (API)/American Indian/Alaska Natives (AN/AI)], marital status (married, unmarried, unknown), and insurance status (public, private, and none/unknown). Unknown marital and insurance status were retained as distinct categories to improve sample size, rather than excluding these cases from analysis. For geographic factors, county-level rurality (no or yes), county-level persistent poverty (no or yes), and Georgia public health district (Southeast, Southwest, North Central, North, Northeast, Northwest, South, South Central, East Central, LaGrange, Coastal, West Central, North Georgia, Clayton, Cobb-Douglas, Fulton, DeKalb, East Metro). Persistent poverty was defined by using poverty rate 20% or higher in 1990, 2000, 2007-2011, and 2017-2021. For tumor characteristics, late stage at diagnosis (no or yes), high pathological grade (no or yes), and primary site (left or right) were included. Finally, we defined the years of diagnosis as 2000-2004, 2005-2009, 2010-2014, or 2015-2021.

Statistical analysis

Descriptive statistics (e.g., frequencies and relative frequencies) were used to describe age at diagnosis, sex, sociodemographic characteris-

tics, tumor characteristics, and year of diagnosis. We also examined bivariate differences within age at diagnosis in sex, sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis, using chi-square tests. Patients' survival time was measured in months from the date of diagnosis up to 12, 36, and 60 months of follow-up, censored at the date of last contact or death due to other causes. Survival analyses were applied using the Kaplan-Meier method with Log-rank test to compare the survival rates between males

and females and stratified by three ages at diagnosis groups. Further, we performed traditional Cox proportional hazard regression to examine the association between sex, age at diagnosis, and causes-specific survival for CRC at 1-, 3-, and 5-year intervals. Unadjusted and adjusted models were performed to examine the association. Unadjusted models included sex and age at diagnosis only; adjusted models were further adjusted for sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis. Finally, we performed the stratify analyses to examine the relationship of sex with EOCRC mortality at three intervals across three age groups. All models were adjusted for sociodemographic characteristics, tumor characteristics, geographic factors, and year of diagnosis. To assess potential bias, sensitivity analyses were conducted by excluding cases with unknown marital and/or insurance status.

To elucidate the risk of EOCRC death in specific timeframe, we performed additional analyses by using piecewise Cox regression models with three follow-up time intervals (0-1 year, 1-5 years, 5+ years). The piecewise Cox model allows the hazard ratio (HR) to vary across different time intervals, which can overcome the limitation of traditional Cox model with constant HR assumption. All results were reported using HRs and the associated 95% confidence intervals (CIs). SAS Version 9.4, SAS Institute Inc., Cary, North Carolina was used to conduct

all analyses. The level of statistical significance was set at an alpha level of 0.05 and the *p*-values were based on two-sided probability tests.

Results

In **Table 1**, the majority of EOCRC patients were aged 40-49 years (72.9%). Many were male (51.6%), were White (57.0%), were married (53.5%), had private insurance (44.6%), living in non-poverty (83.3%) or rural areas (81.5%), had no late stage at diagnosis (83.3%), had no high pathological grade (98.6%), had left-side CRC (68.5%), and were diagnosed during 2015-2020 (36.7%). LaGrange and Fulton districts (8.8% each) and Cobb-Douglas (8.5%) had the highest percentage of patients. Further, there were more female EOCRC patients diagnosed at age of 18-29 years while majority male patients diagnosed at age of 40-49 years (*p*-value =0.073).

Survival analysis

Overall, male patients demonstrated the lower 1- (89.4% vs. 91.9%), 3- (75.7% vs. 79.2%), and 5-year (69.7% vs. 74.3%) survival time than female patients (all *p*-value <0.001). 5-year survival rates were lower among male patients aged 18-29 years (74.5% vs. 81.3% in female patients, *p*-value =0.029; **Figure 2**), aged 30-39 years (70.1% vs. 74.8% in female patients, *p*-value =0.004; **Figure 3**), and aged 40-49 years (69.2% vs. 73.6% in females, *p*-value <0.001; **Figure 4**). Male patients also demonstrated the lower survival rates at 1- and 3-year survival (**Figures 2-4**).

In **Table 2**, results from unadjusted and adjusted models were similar for 5-year intervals. In the adjusted model, we observed that CRC patients aged 30-39 and 40-49 years were 28% (HR, 1.28; 95% CI, 1.08-1.52) and 33% (HR, 1.33; 95% CI, 1.13-1.56) more likely to die from CRC compared to patients aged 18-29, respectively. However, results from unadjusted and adjusted models were dissimilar for 3- and 1-year intervals. When adjusting for all covariates, we found that CRC patients aged 30-39 (HR, 1.21; 95% CI, 1.00-1.45) and 40-49 years were more likely to die from CRC at 3- (30-39 years: HR, 1.21; 95% CI, 1.00-1.45; 40-49 years: HR, 1.27; 95% CI, 1.07-1.51) and 1-year intervals (30-39 years: HR, 1.32; 95% CI, 1.00-1.76; 40-49 years: HR, 1.30; 95% CI,

1.00-1.69). Further, in full adjusted models, male patients demonstrated the greater risk of CRC death for 5-, 3-, and 1-year than female patients by 24% (HR, 1.24; 95% CI, 1.15-1.32), 22% (HR, 1.22; 95% CI, 1.13-1.31), and 34% (HR, 1.34; 95% CI, 1.19-1.31), respectively. The interaction between sex and age at diagnosis were not observed for three survival time-frames. Finally, our sensitivity analysis excluding unknown marital status and insurance status demonstrated similar results with full models (**Supplementary Table 1**).

As shown in **Table 3**, we examined the association between sex and 5-, 3-, and 1-year survival for CRC when stratified by three age groups. Regardless of survival intervals, male aged 30-39 years were more likely to die from CRC at 5- (HR, 1.27; 95% CI, 1.09-1.48), 3- (HR, 1.26; 95% CI, 1.06-1.49), and 1-year (HR, 1.40; 95% CI, 1.08-1.82) intervals, respectively. Similarly, male patients aged 40-49 years were more likely to die from CRC at 5- (HR, 1.22; 95% CI, 1.13-1.33), 3- (HR, 1.20; 95% CI, 1.10-1.32), and 1-year (HR, 1.33; 95% CI, 1.16-1.53) intervals than their female counterparts, respectively. Average survival months was also lower in male patients than female patients at 1-, 3-, and 5-year intervals for 30-39 and 40-49 age groups.

In our piecewise Cox regression models, we observed that the risk of CRC death was 26% and 35% higher for those aged 30-39 and 40-49 between one to five years post diagnosis, respectively, when compared to patients aged 18-29 years, after adjusting for all covariates of interest (**Table 4**). Male patients were more likely to die from CRC regardless of survival intervals by 19%-34%. As shown in **Table 5**, we found that male patients aged 30-39 years had greater risk of CRC death within 1 year interval by 33% (HR, 1.33; 95% CI, 1.02-1.75). Regardless of survival interval, male patients aged 40-49 were also associated with increased risk of CRC death by 17%-38%.

Discussion

Our findings revealed that sex and age trend to be important factors on EOCRC mortality despite we adjusted for important covariates. We found that male patients aged 30-39 and 40-49 years were more likely to die from CRC by 20%-40% regardless of survival intervals. A

Sex and age related differences in EOCRC mortality

Table 1. Characteristics of colorectal cancer patients by age at diagnosis in Georgia (n=11,935)

	Total (n=11,935)	18-29 (n=767, 6.4%)	30-39 (n=2,469, 20.7%)	40-49 (n=8,699, 72.9%)	P-value
Sex					0.073
Male	6,155 (51.6%)	376 (49.0%)	1,239 (50.2%)	4,540 (52.2%)	
Female	5,780 (48.4%)	391 (51.0%)	1,230 (49.8%)	4,159 (47.8%)	
Sociodemographic characteristics					
Race					<0.001
White	6,798 (57.0%)	442 (57.6%)	1,391 (56.3%)	4,965 (57.1%)	
Black	4,150 (34.8%)	236 (30.8%)	827 (33.5%)	3,087 (35.5%)	
Hispanic	655 (5.5%)	62 (8.1%)	172 (7.0%)	421 (4.8%)	
API/AN/AI	332 (2.8%)	27 (3.5%)	79 (3.2%)	226 (2.6%)	
Marital status					<0.001
Married	6,383 (53.5%)	176 (23.0%)	1,326 (53.7%)	4,881 (56.1%)	
Unmarried	4,746 (39.8%)	538 (70.1%)	972 (39.4%)	3,236 (37.2%)	
Unknown	806 (6.8%)	53 (6.9%)	171 (6.9%)	582 (6.7%)	
Insurance					<0.001
Public	2,129 (17.8%)	180 (23.5%)	460 (18.6%)	1,489 (17.1%)	
Private	5,322 (44.6%)	319 (41.6%)	1,057 (42.8%)	3,946 (45.4%)	
None/Unknown	4,484 (37.6%)	268 (34.9%)	952 (38.6%)	3,264 (37.5%)	
Geographic factors					
Poverty					0.202
No	9,937 (83.3%)	711 (92.7%)	2,309 (93.5%)	8,043 (92.5%)	
Yes	1,998 (16.7%)	56 (7.3%)	160 (6.5%)	656 (7.5%)	
Rurality					0.309
No	9,730 (81.5%)	633 (82.5%)	2,034 (82.4%)	7,063 (81.2%)	
Yes	2,205 (18.5%)	134 (17.5%)	435 (17.6%)	1,636 (18.8%)	
Public health district					0.080
Southeast	535 (4.5%)	41 (5.4%)	109 (4.4%)	385 (4.4%)	
Southwest	503 (4.2%)	21 (2.7%)	90 (3.7%)	392 (4.5%)	
North Central	633 (5.3%)	48 (6.3%)	120 (4.9%)	465 (5.4%)	
North	789 (6.6%)	40 (5.2%)	175 (7.1%)	574 (6.6%)	
Northeast	563 (4.7%)	41 (5.4%)	126 (5.1%)	396 (4.6%)	
Northwest	798 (6.7%)	44 (5.7%)	181 (5.1%)	573 (6.6%)	
South	314 (2.6%)	20 (2.6%)	71 (2.9%)	223 (2.6%)	
South Central	203 (1.7%)	10 (1.3%)	42 (1.7%)	151 (1.7%)	
East Central	574 (4.8%)	29 (3.8%)	113 (4.6%)	432 (5.0%)	
LaGrange	1,044 (8.8%)	71 (9.3%)	199 (8.1%)	774 (8.9%)	
Coastal	527 (4.4%)	45 (5.9%)	106 (4.3%)	376 (4.3%)	
West Central	437 (3.7%)	23 (3.0%)	80 (3.2%)	334 (3.8%)	
North Georgia	523 (4.4%)	26 (3.4%)	104 (4.2%)	393 (4.5%)	
Clayton	366 (3.1%)	22 (2.9%)	76 (3.1%)	268 (3.1%)	
Cobb-Douglas	1,013 (8.5%)	61 (8.0%)	201 (8.1%)	751 (8.6%)	
Fulton	1,047 (8.8%)	88 (11.5%)	226 (9.2%)	733 (8.4%)	
DeKalb	827 (6.9%)	51 (6.7%)	191 (7.7%)	585 (6.7%)	
East Metro	1,239 (0.4%)	86 (11.2%)	259 (10.5%)	894 (10.3%)	
Tumor characteristics					
Late stage at diagnosis					0.037
No	9,937 (83.3%)	664 (86.6%)	2,044 (82.8%)	7,229 (83.1%)	
Yes	1,998 (16.7%)	103 (13.4%)	425 (17.2%)	1,470 (16.9%)	
High pathological grade					0.595
No	11,770 (98.6%)	758 (98.8%)	2,430 (98.4%)	8,582 (98.7%)	
Yes	165 (1.4%)	9 (1.2%)	39 (1.6%)	117 (1.3%)	

Sex and age related differences in EOCRC mortality

Primary site					<0.001
Left	8,180 (68.5%)	371 (48.4%)	1,685 (68.3%)	6,124 (70.4%)	
Right	3,755 (31.5%)	396 (51.6%)	784 (31.8%)	2,575 (29.6%)	
Year of diagnosis					<0.001
2000-2004	2,330 (19.5%)	104 (13.6%)	507 (20.5%)	1,719 (19.8%)	
2005-2009	2,574 (21.6%)	129 (16.8%)	526 (21.3%)	1,919 (22.1%)	
2010-2014	2,656 (22.3%)	154 (20.1%)	507 (20.5%)	1,995 (22.9%)	
2015-2020	4,375 (36.7%)	380 (37.6%)	929 (37.6%)	3,066 (35.3%)	

Abbreviations: API, Asian/Pacific Islander; AI/AN, American Indian/Alaska Natives.

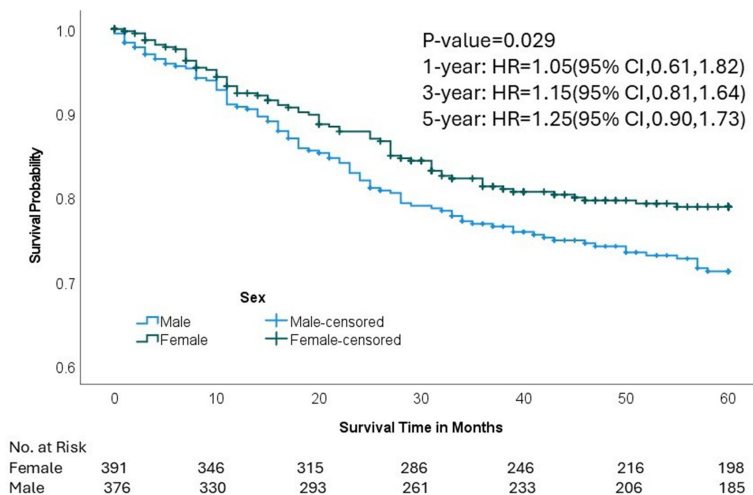


Figure 2. Kaplan-Meier curve of colorectal cancer survival at 18-29 age group.

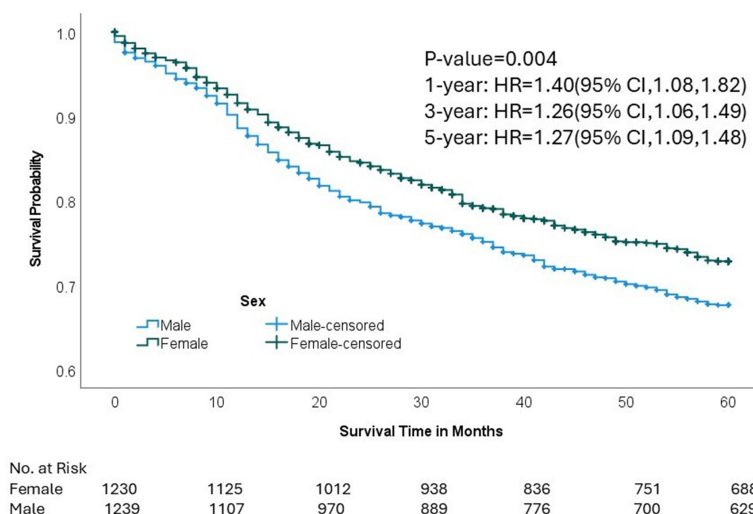


Figure 3. Kaplan-Meier curve of colorectal cancer survival at 30-39 age group.

significant higher estimate of EOCRC mortality at 1-year interval was observed for males aged 30-39 years. Such evidence highlights the

need for prioritizing prevention and treatment strategies for males aged 30-39 years in Georgia.

Overall, we found that older age was associated with greater risk of death from CRC regardless of survival intervals by 21%-33%. Similar to our findings, a recent study reported that older patients (30-39 and 40-49 age groups) were more likely to die from non-cancer causes [18]. However, this study did not find the significant difference for cause-specific death for EOCRC [18]. This discrepancy may be explained by the different geographic populations. In particular, our population is from a single state (Georgia) with a large number of underserved communities that have been considered as hotspots of EOCRC mortality [21]. Several regions in Georgia are considered as medically underserved areas [26]. Living in socioeconomically disadvantaged neighborhoods or medically underserved areas were also more likely to die from CRC death by 15-25% [27, 28]. More importantly, the impact of socioeconomically disadvantaged characteristics (e.g., living in rural or persistent

poverty areas) was more pronounced for EOCRC by 30% [24]. Despite the evidence, in our multivariable analysis, we did not find the sig-

Sex and age related differences in EOCRC mortality

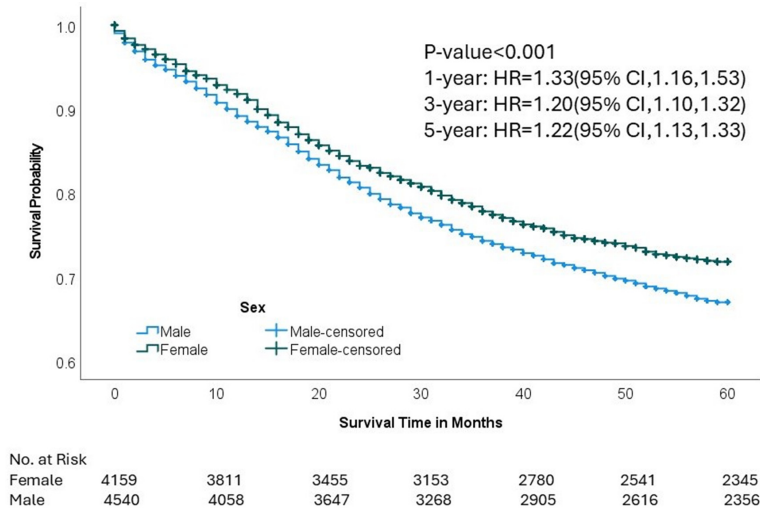


Figure 4. Kaplan-Meier curve of colorectal cancer survival at 40-49 age group.

analysis, which are known to influence CRC survival outcomes. Additionally, variations in patient demographics, socioeconomic factors, and healthcare systems are likely to contribute to these differences, underscoring the need to examine specific populations to better understand the factors influencing health outcomes. Despite our findings being consistent with prior literature in general, none of these studies considered both sex and age at diagnosis for EOCRC survival. Thus, our findings can add to the existing evidence by specifying sex and age population.

nificant impact of rurality or poverty on CRC mortality regardless of time intervals. Majority of young patients tend to live in non-rural or poverty areas (**Table 1**). Future studies explore the other barriers (e.g., lack of awareness of CRC risk) may further elucidate this phenomenon.

Further, we found that male patients were associated with increased risk of CRC death regardless of survival intervals by 22%-34% compared to females. The survival rates were also lower for males than females overall and for males aged 30-39 and 40-49 years. In particular, findings from our piecewise Cox models further confirmed the CRC death fallen in 1-5 years interval for 30-49 age groups and male patients (**Table 4**). In line with prior literature, Afify and colleagues reported that the 1-year, 3-year, and 5-year overall survival rates for young males (89.1%, 73.8%, 65.7%) were lower than young females (91.3%, 76.9%, 69.9%) [18]. In the same study, authors also reported that males were associated with worse cause-specific survival for EOCRC by 15% [18]. However, a study from UK revealed that males had slightly better 1-year survival than females, but the 5-year survival appeared similar between males and females [29]. The discrepancy between our findings and those of the UK study may be attributed to the latter's lack of adjustment for key covariates - such as sociodemographic factors, tumor characteristics, and geographic variables - in multivariable

In stratified analysis, we found the higher estimates of EOCRC death was observed in male patients aged 30-39 years at 1-year interval by 41%, compared to female patients aged 30-39 years. This phenomenon also confirmed by our piecewise Cox models with 33% increased risk of EOCRC death at 0-1-year interval for male patients aged 30-39 years (**Table 5**). Since no studies have examined EOCRC mortality across different time intervals while simultaneously accounting for sex and age-related differences, direct comparisons with previous literature are not feasible. Yet, by using SEER program, Afify and colleagues reported that male aged 30-39 and 40-49 years were 1.8-3.2-fold more likely to die from non-cancer related causes [18]. Several factors such as molecular and genetic factors and lifestyle may be attributed to the unfavorable survival in males [30]. For example, males usually have higher smoking [31] and heavier alcohol consumption rates compared to females [32]. Males are also more likely to consume meat, red meat, and processed meat than females [33]. They also tend to have higher relative weight or body mass index (BMI), which is considered a potential risk factor for CRC [33]. All these risk factors associated with worse health behaviors in males may explain the poorer cause-specific survival for EOCRC observed in our study, particularly at 1-year interval in our analysis. This is also particular true for Georgia because nearly half of cancer deaths in Georgia are linked to modifiable

Sex and age related differences in EOCRC mortality

Table 2. Association between age at diagnosis, sex, and colorectal cancer survival time

	1-year survival		3-year survival		5-year survival	
	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)
Age at diagnosis						
18-29 years	Reference	Reference	Reference	Reference	Reference	Reference
30-39 years	1.19 (0.90, 1.58)	1.32 (1.00, 1.76)	1.12 (0.94, 1.35)	1.21 (1.00, 1.45)	1.21 (1.03, 1.44)	1.28 (1.08, 1.52)
40-49 years	1.15 (0.89, 1.49)	1.30 (1.00, 1.69)	1.17 (0.99, 1.39)	1.27 (1.07, 1.51)	1.25 (1.14, 1.31)	1.33 (1.13, 1.56)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.34 (1.19, 1.51)	1.34 (1.19, 1.51)	1.21 (1.12, 1.30)	1.22 (1.13, 1.32)	1.22 (1.14, 1.31)	1.24 (1.16, 1.33)
P-value for interaction	0.629	0.735	0.835	0.877	0.938	0.879

Abbreviations: HR, hazard ratio; CI, confidence interval. Italicized text indicates statistically significant results. Notes: Unadjusted model includes and age at diagnosis and sex only; Adjusted model was further adjusted for sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis.

Table 3. Association between sex and colorectal cancer survival time by age at diagnosis

	1-year survival		3-year survival		5-year survival	
	Survival time Mean (SD)	HR (95% CI)	Survival time Mean (SD)	HR (95% CI)	Survival time Mean (SD)	HR (95% CI)
18-29						
Female	11.0 (2.9)	Reference	29.4 (11.4)	Reference	43.1 (20.9)	Reference
Male	10.9 (3.1)	1.05 (0.61, 1.82)	28.7 (11.9)	1.15 (0.81, 1.64)	42.1 (21.6)	1.25 (0.90, 1.73)
30-39						
Female	11.3 (2.3)	Reference	30.5 (10.3)	Reference	45.5 (19.9)	Reference
Male	11.1 (2.8)	1.40 (1.08, 1.82)	29.2 (11.4)	1.26 (1.06, 1.49)	43.0 (21.1)	1.27 (1.09, 1.48)
40-49						
Female	11.3 (2.4)	Reference	30.5 (10.3)	Reference	45.4 (19.9)	Reference
Male	11.1 (2.7)	1.33 (1.16, 1.53)	29.5 (11.1)	1.20 (1.10, 1.32)	43.6 (20.8)	1.22 (1.13, 1.33)

Abbreviations: HR, hazard ratio; CI, confidence interval. Italicized text indicates statistically significant results. Notes: All models were further adjusted for sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis.

Table 4. Association between age at diagnosis, sex, and colorectal cancer survival time (0-1, 1-5, and 5+ Years)

	0-1-year survival		1-5-year survival		5+-year survival	
	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)
Age at diagnosis						
18-29 years	Reference	Reference	Reference	Reference	Reference	Reference
30-39 years	1.12 (0.84, 1.50)	1.25 (0.94, 1.67)	1.22 (0.99, 1.50)	1.26 (1.02, 1.56)	0.76 (0.51, 1.12)	0.80 (0.54, 1.19)
40-49 years	1.08 (0.83, 1.41)	1.23 (0.94, 1.61)	1.30 (1.07, 1.58)	1.35 (1.11, 1.64)	1.01 (0.71, 1.43)	1.11 (0.78, 1.58)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.32 (1.16, 1.49)	1.32 (1.17, 1.50)	1.17 (1.07, 1.27)	1.19 (1.10, 1.29)	1.31 (1.12, 1.53)	1.34 (1.15, 1.57)

Abbreviations: HR, hazard ratio; CI, confidence interval. Italicized text indicates statistically significant results. Notes: Unadjusted model includes and age at diagnosis and sex only; Adjusted model was further adjusted for sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis.

behavioral risk factors such as obesity (BMI ≥ 30) and smoking [34-38]. Such evidence highlights the need for examining various factors (e.g., health behaviors) associated with these pheromones in Georgia, particularly for males aged 30-39 years.

The main strength of this research is the first to investigate sex and age-related differences in EOCRC survival while considering three survival intervals for EOCRC by using traditional and piecewise Cox regression models. By using two different approaches, we are able to confirm

Sex and age related differences in EOCRC mortality

Table 5. Association between sex and colorectal cancer survival time by age at diagnosis (0-1, 1-5, and 5+ Years)

	0-1-year survival		1-5-year survival		5+-year survival	
	# of death (%)	HR (95% CI)	# of death (%)	HR (95% CI)	# of death (%)	HR (95% CI)
18-29						
Female	28 (7.3%)	Reference	46 (4.1%)	Reference	16 (1.2%)	Reference
Male	31 (8.5%)	1.01 (0.58, 1.76)	63 (6.1%)	1.39 (0.93, 2.10)	17 (1.3%)	0.55 (0.21, 1.42)
30-39						
Female	96 (7.9%)	Reference	211 (5.7%)	Reference	51 (0.9%)	Reference
Male	123 (10.2%)	1.33 (1.02, 1.75)	235 (6.7%)	1.20 (0.99, 1.45)	57 (1.1%)	1.23 (0.84, 1.81)
40-49						
Female	308 (7.5%)	Reference	773 (6.2%)	Reference	218 (1.1%)	Reference
Male	440 (9.9%)	1.34 (1.15, 1.55)	921 (7.1%)	1.17 (1.06, 1.29)	285 (1.5%)	1.37 (1.15, 1.64)

Abbreviations: HR, hazard ratio; CI, confidence interval. Italicized text indicates statistically significant results. Notes: All models were further adjusted for sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis.

the higher risk of EOCRC death in male patients aged 30-39 years within 1 year interval. This finding has important implications for this age group. Tailored education programs to raise awareness of CRC risk, along with targeted prevention strategies such as risk assessment or shortening follow-up time, may be beneficial. More research should also further investigate boarder factors such as biological, behavioral, or healthcare access contributing to early mortality in this group. Despite the strengths, there were a few limitations that should be noted. Although the study has accounted for many covariates in analyses, the Georgia cancer registry database did not collect information on individual income, education level, healthy lifestyle factors (e.g., body mass index, smoking, and alcohol consumption), and concomitant diseases [39, 40]. For example, obesity is strongly associated with EOCRC risk and may lead to the greater risk of CRC-related death [41-43]. Future research should integrate multiple data sources to capture relevant factors and further clarify the underlying survival disparities. Second, although our study population is from Georgia, which has similar demographic characteristics in the Southeast states [25], generalizability issue may still exist. However, our study highlights the value of focusing on more narrowly defined populations that may be affected by similar socioeconomic factors, healthcare systems and other demographic characteristics (e.g., racial minorities). This approach can serve as a foundation for studies involving different geographic locations, including Southeast states (e.g., South Carolina), particularly given that 92% of coun-

ties in South have been identified as EOCRC hotspots [21]. Further, we were unable to include potential barriers to care (e.g., lack of awareness of cancer risk, lack of healthcare access for treatment resources) that may partly explain our findings regarding the higher EOCRC mortality for male patients and those aged 30-49 years. We also did not include factors associated with cancer prevention, such as family history of CRC. Finally, the retrospective nature of the study relies on existing data, which may be subject to biases such as incomplete records or inaccuracies in coding.

Conclusion

Age related disparities in EOCRC mortality were observed among male patients. Male patients aged 30-49 years demonstrated the greater risk of EOCRC death at 1-, 3- and 5- year intervals. In particular, the greater risk of EOCRC mortality at 1-year interval was observed among males aged 30-39 years. Prioritizing prevention and treatment strategies may reduce the risk of 1-year EOCRC mortality for males and 30-39 age group. Improving awareness of CRC risk and promoting healthy lifestyle for these groups may also be beneficial. Future research should evaluate multifaceted factors and identify/address specific barriers among young males to reduce disparities in EOCRC mortality in Georgia.

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Disclosure of conflict of interest

None.

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Sex and age related differences in EOCRC mortality

Supplementary Table 1. Association between age at diagnosis, sex, and colorectal cancer survival time: Reduced (n=8,198) and Full models (n=11,935)

	1-year survival		3-year survival		5-year survival	
	Reduced model HR (95% CI)	Full model HR (95% CI)	Reduced model HR (95% CI)	Full model HR (95% CI)	Reduced model HR (95% CI)	Full model HR (95% CI)
Age at diagnosis						
18-29 years	Reference	Reference	Reference	Reference	Reference	Reference
30-39 years	1.31 (0.98, 1.75)	1.32 (1.00, 1.76)	1.20 (1.00, 1.44)	1.21 (1.00, 1.45)	1.23 (1.00, 1.51)	1.28 (1.08, 1.52)
40-49 years	1.31 (1.00, 1.72)	1.30 (1.00, 1.69)	1.27 (1.07, 1.51)	1.27 (1.07, 1.51)	1.34 (1.11, 1.61)	1.33 (1.13, 1.56)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.32 (1.17, 1.49)	1.34 (1.19, 1.51)	1.21 (1.12, 1.30)	1.22 (1.13, 1.32)	1.22 (1.12, 1.32)	1.24 (1.16, 1.33)

Abbreviations: HR, hazard ratio; CI, confidence interval. Italicized text indicates statistically significant results. Notes: All models were adjusted for age at diagnosis, sex, sociodemographic characteristics, geographic factors, tumor characteristics, and year of diagnosis. Reduced models excluding unknown marital status and/or insurance status.