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ORIGINAL ARTICLE

Incidence and characteristics of young-onset colorectal cancer in the United States: An analysis of SEER data collected from 1988 to 2013

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KEYWORDS
Colorectal cancer;
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Summary
Background: The incidence of colorectal cancer (CRC) has significantly increased in adults < 50 years old who are below the screening age.
Objectives: The primary objective was to evaluate the age-standardized incidence (ASI) of young-onset CRC from 1988 to 2013. The secondary objective was to assess factors associated with cancer-specific death (CSD).
Methods: We accessed data of 64,854 CRC patients (20—49 years old) from the United States Surveillance, Epidemiology, and End Results Program (SEER) database.
Results: A gradual increase in the ASI of CRC in the study population was found: from 3.59/100,000 males in 1988 to 5.21/100,000 males in 2013, and from 3.15/100,000 females in 1988 to 4.45/100,000 females in 2013. ASI adjusted by race revealed a relatively pronounced increase in the white population compared to African American and other races, with an increase from 3.07/100,000 persons in 1988 to 4.79/100,000 persons in 2013. Males had a 19% higher likelihood of CRC-related death compared to females [hazard ratio (HR) = 1.19, 95% confidence interval (CI): 1.16—1.23], and African American had a 1.34-fold higher likelihood of CRC-related death compared to whites (95% CI: 1.28—1.39). CRC-related death was significantly higher in patients with signet ring-cell histology (HR = 1.56, 95% CI: 1.45—1.68), compared to patients with adenocarcinoma. Male gender, and advanced stage predicted a higher likelihood of CRC-related death in African Americans compared to the whole population. Signet ring-cell histology, advanced stage, and advanced grade were significantly associated with CRC-related death in African-American patients.

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Conclusion: This study corroborates emerging data that the (ASI) of young-onset CRC is increasing. It also identified factors associated with cancer-specific death in this population that may aid in targeting screening strategies for adults < 50 years old.

Introduction

Routine screening of adults > 50 years of age has contributed to a decline in the incidence of colorectal cancer (CRC) in this population [1—3]. However, recent data have reported an increase in CRC incidence in adults < 50 years old, who are typically below the screening age [4]. In the United States, the incidence of CRC in adults < 50 years old steadily increased, at a rate of 2.1% per year, from 1992 through 2012 [2]. Additionally, some registries reported a rising incidence of CRC even among young adults 20—39 years of age, although the absolute incidence in this age group remains far lower than the incidence in adults > 50 years old [5,6]. These results suggested that it may be useful to lower the screening age for CRC [3,7]. Recently, the American Center Society has adjusted its guidelines, making the qualified recommendation that adults at average risk get screening starting at age 45 [8], but the United States Preventive Services Task Force guidelines are unchanged.

Younger CRC patients reportedly have a higher risk of mucinous tumors, signet ring-cell tumors, poorly differentiated tumors, and anaplastic tumors, and receive more aggressive treatment than do older patients [9,10]. Although a study showed that younger patients had a significantly better 5-year survival rate than that of patients > 50 years old [11], other data suggested that the more aggressive features seen in young-onset CRC were associated with increased mortality over time compared to that of older patients [12]. Additionally, studies have reported racial disparities in the incidence and survival of patients with young-onset CRC [13,14]. Minority groups including African Americans, Asian/Pacific Islanders, Hispanics, and American Indian/Alaska natives below the age of 50 were shown to have a higher risk for early-onset CRC [15].

The objective of the present study was to analyze the epidemiologic trend, disease patterns, and survival outcomes of young-onset CRC in the United States between 1988 and 2013, using information accessed from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) database.

Methods

Data source

Data for this study were obtained from the SEER database released in April 2016, based on the November 2015 submission. The SEER database provides information on cancer incidence and survival in the United States, using data collected from population-based registries, which cover approximately 28% of the country's population. Data in the SEER registries include patient demographics, primary tumor site, tumor morphology, stage at diagnosis, treatment, and follow-up status. The database is also linked to information on Medicare enrolment and Medicare claims, along with healthcare utilization and cost information for beneficiaries with cancer in the United States. Since the SEER data are de-identified, this study did not require either Institutional Review Board approval or informed consent by the study subjects. We obtained permission to access the research data files of the SEER program (reference number, 14876-Nov2015).

Study objectives

The primary objective of this study was to determine the age-standardized incidence (ASI) of young-onset CRC between 1988 and 2013. The secondary objective was to evaluate factors associated with cancer-specific death (CSD), which was indicated as ''cause of death'' in the SEER database.

Independent variables for comparison included patient demographic data (age at diagnosis, sex, race/ethnicity, marital status, and geographic region categorized by the SEER registry), and clinical characteristics of the malignancy (histological diagnosis, American Joint Committee on Cancer TNM stage and grade).

Statistical analysis

The United States population based on the 2000 census was selected as the standard population for calculation of ASI. The Fine and Gray's model with cumulative incidence function was performed to determine competing risks associated with CSD, and to estimate hazards ratios along with their corresponding 95% confidence intervals. A Cox proportional hazard regression model was used to analyze cause-specific hazard of prognostic factors for survival outcomes. Variables having a *P*-value < 0.05 in the univariate analysis were evaluated by multiple analysis with stepwise selection. All statistical tests were 2-sided and performed with SAS version 9.4 (SAS Inc., Cary, NC, USA).

Results

Study population

We accessed data of patients diagnosed with primary CRC based on International Classification of Diseases for Oncology, Third Revision (ICD-O-3) codes of primary site tumors (C180—209, 260). The SEER database (1973—2013) includes the data of 944,364 CRC patients. This study collected data

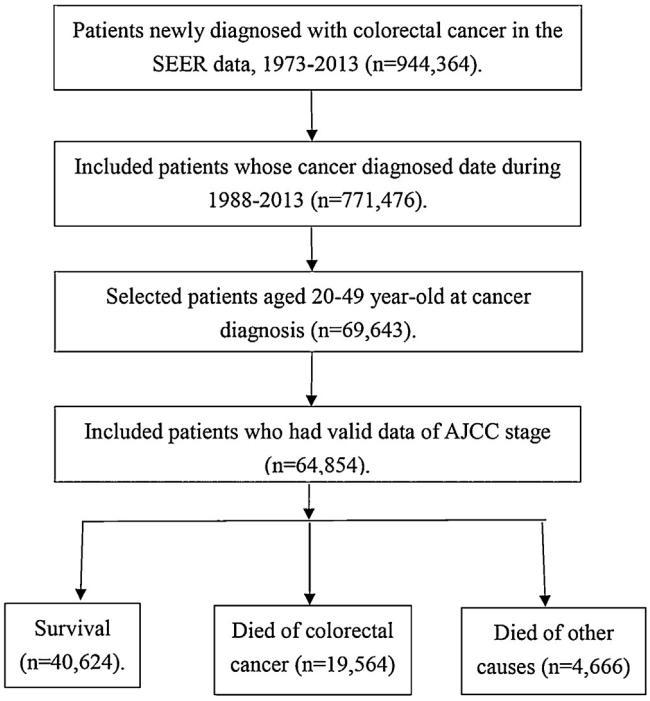

Figure 1 Flow diagram of study design.

of patients diagnosed between January 1, 1988 and December 31, 2013 in the SEER-18 registry (n = 771,476). Data were collected for patients who were 20—49 years old at the time of diagnosis (n = 69,643), and the final analysis included patients with valid data for American Joint Committee on Cancer stage (n = 64,854 patients).

The patient selection strategy for this study is described in Fig. 1. The final analysis included 64,854 patients who met the inclusion/exclusion criteria. The demographic and clinical characteristics of the study patients are described in Table 1. The study population was comprised of 52.7% males and 47.3% females. A majority of the study population (47.3%) was 45—49 years old, while 40.7% of the patients were between 35 and 44 years old. CRC was the first primary cancer in 92.8% of patients. Most of patients were white (73.6%), and most came from the western region of the SEER registry (51.9%). Most of the patients had adenocarcinoma (86.3%), and 56.3% had stage III or IV disease. Tumors in more than half the patients (55.6%) had grade II differentiation.

The CRC ASI of the whole US population for each year by age group is shown in Supplemental Table 1 and that of persons between 20 and 50 years of age in Supplemental Table 2.

Fig. 2A illustrates that in contrast to the nationwide decline in ASI over the past 26 years, there was a gradual increase in the ASI of CRC in the study population: the ASI of CRC grew from 3.59/100,000 males in 1988 to 5.21/100,000 males in 2013, and from 3.15/100,000 females in 1988 to 4.45/100,000 females in 2013. Fig. 2B illustrates that ASI adjusted by race showed a relatively pronounced increase in the white population compared to African American and other races, with an increase from 3.07/100,000 persons in 1988 to 4.79/100,000 persons in 2013.

Table 1 Demographic and clinical characteristics of study patients.

Variables	Category	Number	%
Age at diagnosis, years	20—24	900	1.4
	25—29	2200	3.4
	30—34	4676	7.2
	35—39	9082	14.0
	40—44	17342	26.7
	45—49	30654	47.3
Sex	Male	34200	52.7
	Female	30654	47.3
Marital status	Single	16395	25.3
	Married	45082	69.5
	Unknown	3377	5.2
Race	White	47756	73.6
	Black	9530	14.7
	Others	7568	11.7
Region of SEER registry	Northeast	9604	14.8
	South	14259	22.0
	North central	7329	11.3
	West	33662	51.9
Histological type	Adenocarcinoma	55923	86.3
	Signet ring-cell	1315	2.0
	Minor subtypes[a]	639	1.0
	Others	6962	10.7
Stage	I	12268	20.8
	II	13510	22.9
	III	18043	30.6
	IV	15161	25.7
Grade	I	5503	8.5
	II	36028	55.6
	III	11369	17.5
	IV	990	1.5
	Unknown or not applicable	10964	16.9
First primary cancer	No	4666	7.2
	Yes	60188	92.8

[a] Minor subtypes include small cell, squamous cell, adenosquamous, medullary, or undifferentiated.

Fig. 3A illustrates that of the four regions of the SEER registry, there was a two-fold increase in the ASI from 1988 to 2013 among registries located in the southern region (2.7/100,000 persons in 1988 and 5.9/100,000 persons in 2013). As illustrated in Fig. 3C, the increase in ASI was mainly in young patients with stage III or above disease in the study population (from 0.91/100,000 stage III patients and 0.75/100,000 stage IV patients in 1988 to 1.37/ 100,000 stage III patients and 1.30/100,000 stage IV patients in 2013).

Table 2 summarizes factors associated with CRC-related death in the study population. According to univariate analysis, the incidence increased progressively in the age groups from 25—29 through 45—49. In multivariate analysis, male patients had a 1.19-fold higher likelihood of CRC-

Table 2 Factors associated with CRC-related death in the whole study population ($n = 64,854$).

	Univariate		Multiple	
Variables	Hazard ratio (95% CI)	***P***	Hazard ratio (95% CI)	***P***
Age, years				
20—24	Reference		Reference	
25—29	0.88 (0.76, 1.02)	0.091	1.01 (0.87, 1.17)	0.876
30—34	0.85 (0.75, 0.98)	**0.020**	1.05 (0.92, 1.2)	0.490
35—39	0.82 (0.72, 0.94)	**0.003**	1.04 (0.91, 1.19)	0.535
40—44	0.81 (0.72, 0.92)	**0.001**	1.09 (0.96, 1.24)	0.195
45—49	0.81 (0.71, 0.91)	**0.001**	1.12 (0.99, 1.27)	0.078
Sex				
Female	Reference		Reference	
Male	1.14 (1.11, 1.17)	**< 0.001**	1.19 (1.16, 1.23)	**< 0.001**
Marital status				
Single	Reference		Reference	
Married	0.75 (0.72, 0.77)	**< 0.001**	0.82 (0.79, 0.84)	**< 0.001**
Unknown	0.64 (0.59, 0.7)	**< 0.001**	0.81 (0.74, 0.88)	**< 0.001**
Race				
White	Reference		Reference	
Black	1.42 (1.37, 1.48)	**< 0.001**	1.34 (1.28, 1.39)	**< 0.001**
Others	1.00 (0.96, 1.05)	0.934	1.00 (0.96, 1.05)	0.889
Region of SEER registry				
West	Reference		Reference	
Northeast	0.91 (0.88, 0.96)	**< 0.001**	0.89 (0.85, 0.93)	**< 0.001**
South	1.08 (1.04, 1.12)	**< 0.001**	1.02 (0.98, 1.06)	0.423
North central	1.01 (0.96, 1.05)	0.753	1.02 (0.98, 1.07)	0.366
Histological type				
Adenocarcinoma	Reference		Reference	
Signet ring-cell	2.96 (2.75, 3.18)	**< 0.001**	1.56 (1.45, 1.68)	**< 0.001**
Minor subtypes	1.42 (1.22, 1.66)	**< 0.001**	1.39 (1.21, 1.60)	**< 0.001**
Others	0.71 (0.66, 0.77)	**< 0.001**	0.85 (0.79, 0.92)	**< 0.001**
Stage				
I	Reference		Reference	
II	2.60 (2.4, 2.82)	**< 0.001**	2.57 (2.37, 2.8)	**< 0.001**
III	5.44 (5.05, 5.86)	**< 0.001**	5.30 (4.91, 5.72)	**< 0.001**
IV	27.25 (25.35, 29.28)	**< 0.001**	29.06 (26.97, 31.31)	**< 0.001**
Grade				
I	Reference		Reference	
II	1.54 (1.44, 1.64)	**< 0.001**	1.22 (1.14, 1.31)	**< 0.001**
III	3.00 (2.79, 3.21)	**< 0.001**	1.82 (1.69, 1.95)	**< 0.001**
IV	3.55 (3.15, 4)	**< 0.001**	2.04 (1.81, 2.29)	**< 0.001**
Unknown or not applicable	2.11 (1.96, 2.28)	**< 0.001**	1.73 (1.6, 1.87)	**< 0.001**

CI: confidence interval.
Bold values indicate statistical significance, $P < 0.05$.

related death compared to that in females (HR = 1.19, 95% CI: 1.16—1.23); married person were less likely to have CRC-related death than were unmarried persons (HR = 0.82, 95% CI:0.79—0.84); and African American patients had a 1.34-fold higher likelihood of CRC-related death than patients of white ethnicity (95% CI: 1.28—1.39); patients in northeast had less risk of CRC-related death than those in west (HR = 0.89, 95%CI: 0.85—0.93). CRC-related death was significantly higher in patients with signet ring-cell cancer (HR = 1.56, 95% CI: 1.45—1.68), and minor subtypes (including small cell, squamous cell, adenosquamous, medullary, and undifferentiated carcinoma) (HR = 1.39, 95% CI: 1.21—1.60) than in patients with adenocarcinoma. There was a direct correlation between cancer stage and likelihood of CRC-related death: Compared to patients with stage I disease, patients with stage II, III, or IV disease had a 2.57-fold (95% CI: 2.37—2.80), 5.30-fold (95% CI: 4.91—5.72), and 29.06-fold (95% CI: 26.97—31.31), respectively, higher likelihood of CRC-related death. Similarly, CRC-related death was significantly higher in patients with advanced tumor grade, or poorer differentiation compared to patients with grade I or well differentiated CRC. The HRs were 1.22 (95% CI: 1.14—1.31) for grade II, 1.82 (95% CI: 1.69—1.95) for grade III, and 2.04 (95% CI: 1.81—2.29) for grade IV CRC.

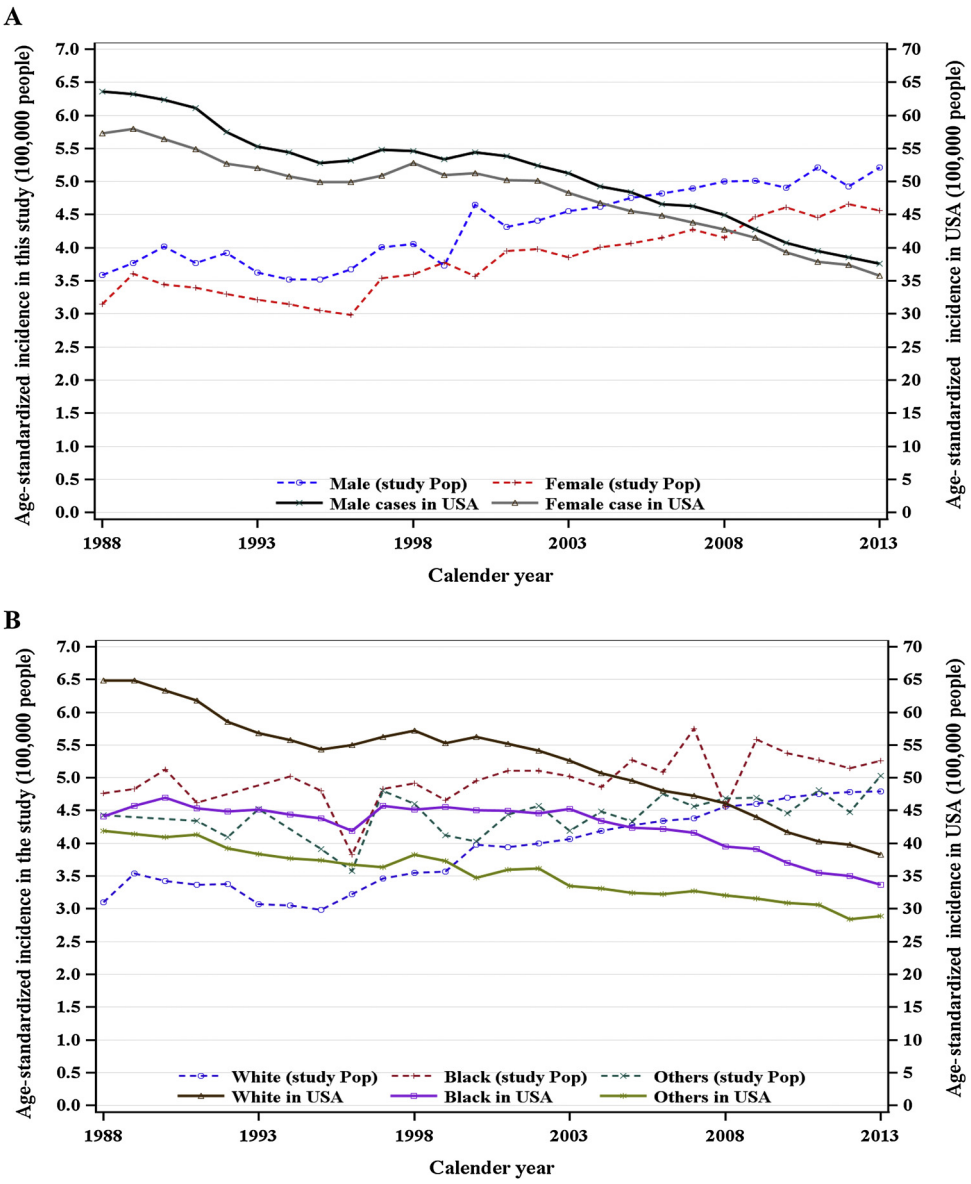

Figure 2 Age-standardized incidences of CRC adjusted to the 2000 United States population (19 age groups), and to the distributions of sex (A) and race (B).

Discussion

The objective of the present study was to analyze the epidemiologic trend, disease patterns, and survival outcomes of young-onset CRC in the United States between 1988 and 2013, using information accessed from the National Cancer Institute's SEER database on 64,854 CRC patients aged who were 20—49 years. The major finding was a gradual increase in the ASI of CRC in this population. ASI adjusted by gender showed:

- an increase in ASI in the white population compared to African American and other races;
- a two-fold increase in the ASI of CRC from person located in southern USA, and;
- an increase in ASI among young patients with stage III or above disease.

Also, we found that sex, race, histological type, stage, and grade were associated with a higher CRC-related mortality: male and advanced stage disease predicted a higher likelihood of CRC-related death in African American patients, whereas being married was associated with a lower likelihood; CRC-related death in African American patients was significantly associated with signet ring-cell histology, late stage and advanced grade.

The incidence of CRC has been shown to be approximately the same in males and females; however, the impact of sex on overall survival remains unclear. While the current analysis showed that the ASI of CRC between 1988—2013 increased in both males and females, males had a 19% higher likelihood of CRC-related death than did females. The analysis also showed that young-onset CRC was most common in the southern region of the registry and least common in the western region, suggesting a potential role for environ-

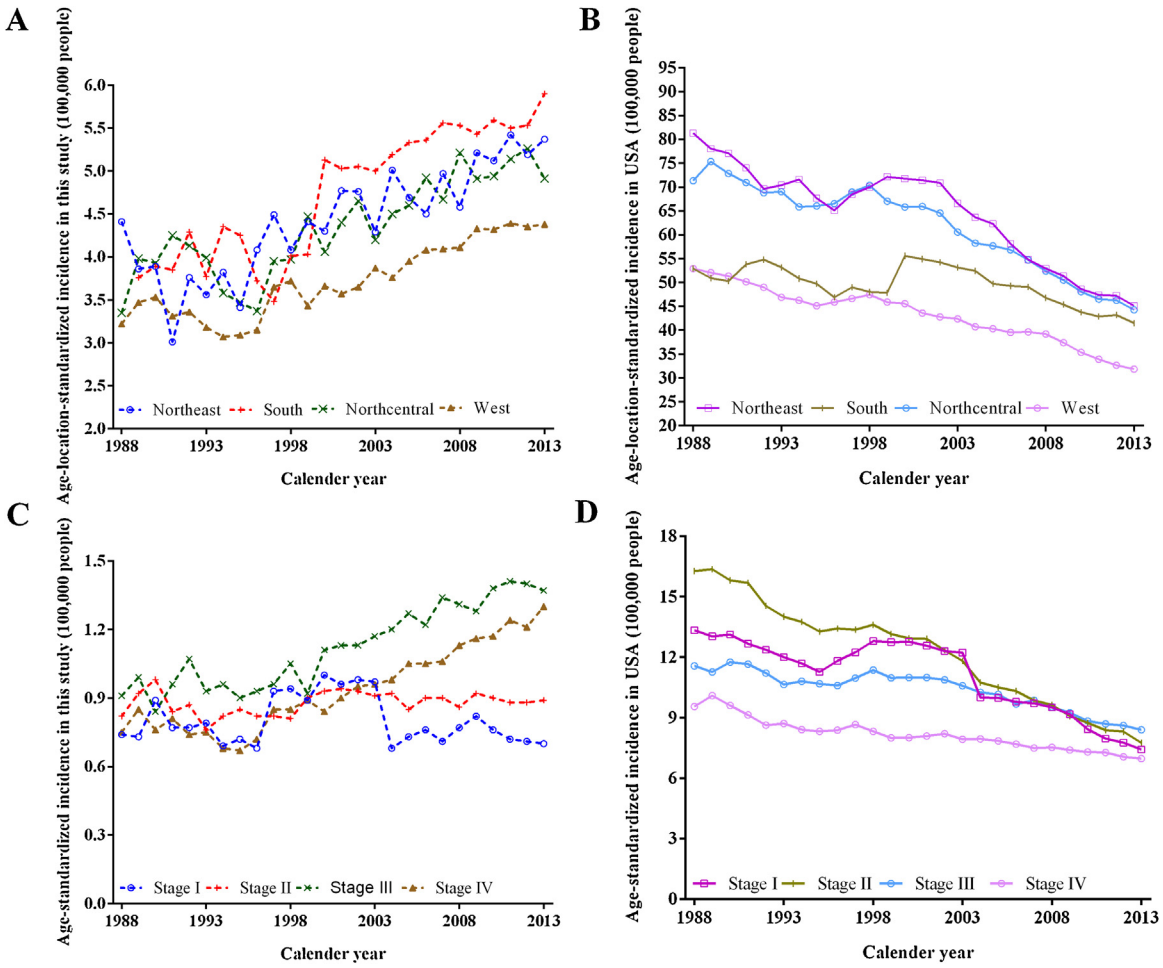

Figure 3 Age-standardized incidences of CRC adjusted to the 2000 United States population (19 age groups), and to location of SEER registry (A and B) and by cancer stage (C and D).

mental factors. With respect to social factors, our data were consistent with a previous report showing that marital status was an independent prognostic factor of survival in patients with CRC [16].

Young-onset CRC has been shown to be more prevalent in non-white populations and among the uninsured and Medicaid-insured populations [9]. While it has not been established, data suggest that the prognosis for CRC in young adults is worse than that in older persons, and that the disease in the young may be a distinct disease [17]. An international collaborative study found that although there was no significant difference in treatment patterns and survival outcomes between younger and older patients with CRC, young-onset disease may be more aggressive than that in older individuals [18]. Li et al. [19] reported that patients 40—59 years old and 60—85 years old with CRC had higher overall survival than did patients 20—39 years of age.

CRC in young patients has been shown to be present at a later stage and to have a significantly longer time-to-diagnosis than CRC older patients [17—19]. Lower screening rates may be the reason for later stage disease in the younger population [12]. Younger CRC patients also have more adenocarcinomas with mucinous and signet ring-cell histology, as well as poorly differentiated histology [9,12], which are features associated with more aggressive disease and worse outcomes [16,20]. Our data were consistent with those of the prior studies.

There is a genetic component to the development of CRC, and relatives of patients with CRC are at higher risk of developing the disease. The SEER database, however, does not contain family history data, and thus we were not able to analyze this aspect of the disease in young adults. Other studies, however, have shown that genetics plays a role in the development of young-onset disease. A cohort study of CRC in persons less than 50 years of age showed that 50% of cancers were associated with a family history of CRC, hereditary CRC syndrome, and inflammatory bowel disease [21]. Other authors have described a sporadic subtype that occurs in the absence of a family history of the disease, and an inherited subtype associated with specific genetic mutations [17,22]. Although it remains unclear whether general screening of individuals under 50 years of age is beneficial or cost-effective [23], Stanesby and Jenkins [24] reported that screening eligibility based on genetic risk profile for age is as efficient as eligibility based on age alone for preventing CRC mortality, and it identifies an additional 7% of the population at sufficient risk to benefit from screening who would not normally be screened given that they are aged under 50 years.

This study has limitations. Although it was a longitudinal analysis, the SEER database only provides data for initial treatment with surgery or radiation therapy. The impact of other treatment modalities on survival was masked and may lead to false interpretations of the results. SEER is a US-specific database, and the results may not be generalizable to other countries. Lastly, the data used for the analysis do not allow for evaluation of causality.

Conclusion

While general screening of younger persons for CRC has not been proven cost-effective, results of this study support the recommendations of screening before age 50. This opinion reflects in part the higher rate of ASI among young patients with stage III or above disease. The trend towards increasing incidence of early-onset CRC in the white population and, in the United States, the higher rates of CRC in younger person in the South than in other regions should be appreciated in developing screening strategies.

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Disclosure of interest

The authors declare that they have no competing interest.

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Wei-bing Wang: Conception and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript; final approval of the manuscript.

Wen-Bin Chen: Conception and design; critical revision of the manuscript; final approval of the manuscript; guarantor of integrity of the entire study.
Jian-Jiang Lin: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript; definition of intellectual content.
Qin-Song Shen: Analysis and interpretation of data; critical revision of the manuscript; final approval of the manuscript; literature research.
Xile Zhou: Drafting of the manuscript; final approval of the manuscript.
Caizhao Lin: Conception and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript; final approval of the manuscript.