Incidence and risk factors for cerebrovascular-specific mortality in patients with colorectal cancer: A registry-based cohort study involving 563298 patients

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Abstract

Background: Colorectal cancer (CRC) is one of the most prevalent diseases and the second leading cause of death worldwide. However, the relationship between CRC and cerebrovascular-specific mortality (CVSM) remains elusive and less is known about the influencing factors associated with CVSM in CRC. Here, we aimed to analyze the incidence as well as the risk factors of CVSM in CRC.

Methods: Patients with a primary CRC diagnosed between 1973 and 2015 were identified from Surveillance Epidemiology and End Results database with follow-up data available until 31 December 2016. Conditional standardized mortality ratios were calculated to compare the incidence of CVSM between CRC patients and the general US population. Univariate and multivariate survival analyses with a competing risk model were used to interrogate the risk factors for CVSM.

Results: A total of 563298 CRC individuals were included. The CVSM in CRC patients was significantly higher than the general population in all age subgroups. Among competing causes of death in patients, the cumulative mortality caused by cerebrovascular-specific diseases steadily increased during study period. While age and surgery positively influenced CVSM on both univariate and multivariate analyses, male patients and those who had radiotherapy, chemotherapy, more recent year (2001-2015) of diagnosis as well as multiple primary or distant tumors experienced a lower risk of CVSM.

Interpretation: Our data suggest a potential role for CRC in the incidence of CVSM and also identify several significant predictors of CVSM, which may be helpful for risk stratification and therapeutic optimization of cerebrovascular-specific diseases in CRC patients.

Key words: Colorectal cancer; Cerebrovascular-specific mortality; Cerebrovascular-specific diseases; Incidence; Risk factors

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Introduction

Colorectal cancer (CRC) ranks as the third most common malignant cancer and the second leading cause of cancer deaths worldwide, with 1.9 million newly diagnosed CRC cases and 935,000 deaths reported in 2020.[1, 2] Due to the growth and aging of the population, the incidence and death rate of CRC continues to increase, which poses a great medical and economic burden for the nation.[3] Therefore, it is imperative to further optimize therapeutic decisions and risk stratification to reduce the mortality of patients.

Previous studies have shown that the occurrence of cerebrovascular-specific diseases (CVSDs) is common in cancer patients.[4] For instance, it has been demonstrated that the incidence rates of stroke in patients with lung cancer and breast cancer were 5.1% and 1.5%, respectively.[5] However, the association between CRC and CVSDs remains to be fully elucidated. Researchers have indicated that CRC is a heterogeneous pathology characterized by a gut microbiota disorder.[6, 7] Despite the small sample size, recent studies have suggested that aberrant gut microbiota components can lead to vascular atherosclerosis, thereby promoting the incidence of cardiovascular-related events.[8, 9] However, whether the dysregulated gut microbiota in CRC could also contribute to an increased risk of CVSDs development requires further validation.

Previously published reports have indicated that CVSDs constitute a major factor related to the mortality of CRC patients. Given the high incidence and mortality rate of CRC in the general population, it is important to identify CRC survivors who are at an elevated risk of cerebrovascular-specific mortality (CVSM) to stratify patients and guide therapeutic optimization, thereby improving the survival and quality of life of patients. In this study, we aimed to analyze the incidence and risk factors for CVSM in a large CRC patient cohort. To this end, we first collected CRC patients from the Surveillance, Epidemiology, and End Results (SEER) database and compared their CVSM to that of the general population. We then used univariate and multivariate analyses with a competing risks model to identify the predictive factors of CVSM for

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these patients.

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Methods and materials

Data sources

In this registry-based retrospective cohort study, we analyzed colorectal cancer (CRC) patient data from the SEER database.[10] This database consists of 21 regional cancer registries, which covers 37% of the US population. It provides detailed clinical information about a large population of cancer patients. The underlying cause of death for cancer patients was coded by the International Classification of Diseases-10 (ICD-10). In addition, the reference cohort represented by the general US population was also obtained from the Centers for Disease Control and Prevention (CDC) database.[11]

Study population

CRC patients were identified as those who were newly diagnosed with colon or rectal cancer with the ICD-10 site codes of C18.0-C18.9, C26.0, C19.9 and C20.9 between 1 January 1973 and 31 December 2015 in the SEER database. We screened a subset of CRC patients by exclusion criteria, and all procedures are shown in **Figure 1**.

We retrieved the clinical data of each patient from the database, which included the following: year of CRC diagnosis (≤ 2000/2001-2005/2006-2015), age at diagnosis (< 50/50-64/65-75/≥ 75 years), sex (female/male), race (white/black/unknown), tumor grade (I-IV), tumor stage (in situ/localized/regional/distant), number of primary tumors (one/multiple), radiotherapy, chemotherapy and tumor site. For the purpose of analysis with a large enough sample size, data on the year of diagnosis and patient age were separated into different subgroups as suggested previously.[12] ‘Multiple tumors’ was defined if a patient was diagnosed with more than one primary tumor when alive, irrespective of whether this disease was CRC or not. Tumor grade and stage were defined by the American Joint Committee on Cancer (AJCC) 6th edition from the SEER database. Tumor sites were classified according to colorectal anatomy.[13] Cerebrovascular-specific diseases (CVSDs) were defined according to the SEER database recode 50060. CVSM was defined as the time from the diagnosis of CRC to

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patient death caused by CVSDs. Patients were followed-up until death or the end of observation in December 2016, whichever occurred first.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation, and categorical variables are expressed as numbers and percentages (%). We estimated cumulative mortality for all causes among CRC patients after diagnosis with a competing risks model. We defined mortalities from CVSDs, CRC, other cancers and other noncancer diseases as competing risks. This method was also used to identify influencing factors associated with CVSM in CRC patients, in which univariate and multivariate survival analyses (only including significant factors in univariate analysis) were performed by calculating the cumulative mortality and hazard ratios (HRs) between different subgroups for each predictor. We calculated the CVSDs and overall conditional standardized mortality ratio (cSMR) in CRC patients relative to general US population among 8 age subgroups (< 50, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80-84 years). Patients aged more than 84 years were not included for analysis due to the lack of these data in the general population from the CDC database. The cSMR was defined as the ratio of CVSD-specific or overall deaths in the CRC group to the estimated number of deaths in the general US population. We determined these age classifications for two reasons. First, given the small number of younger CRC patients, we divided them into a single group to allow for statistical effectiveness. Second, the official mortality statistics of the US population were categorized in exactly the same 5-year steps, making it easier for us to conduct comparative analysis.

All analyses were conducted using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The 95% confidence interval (95% CI) and *P* value were estimated as previously described.[14, 15] All tests were two-sided, and a *P* value of less than 0.05 was considered statistically significant.

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Results

Patient Characteristics

A total of 563298 CRC patients were included in this study with a median age of 68.6 ± 13.1 years. The median follow-up time were 6.67 ± 6.48 years. The sex ratio was basically equal (male, 50.9%). The majority of patients were white (83.3%) and diagnosed beyond the age of 75 years (36.7%). Most patients had one primary tumor (70.7%), a regional tumor stage (41.7%) and a tumor grade of II (66.7%). A total of 94.1% of the patients received surgery, while a small proportion of the patients had chemotherapy (11.6%) or radiotherapy (29.1%). All patient characteristics are detailed in **Table 1.**

Cumulative mortality

Our study found that CVSDs cumulative mortality slightly increased from 1973-2015. CRC had the highest cumulative mortality, followed by other noncancer causes of death in the early period of 1973-2015. However, this trend went in the opposite direction in the middle and late periods (**Figure 2**).

In the univariate analyses, our data showed that CVSDs cumulative mortality was positively associated with age (**Figure 3**) and the year of CRC diagnosis (**Figure 4**), while the tumor grade had an inverse correlation with CVSM (**Figure 5**). In addition, male patients and those who received chemotherapy or radiotherapy experienced a lower CVSDs cumulative mortality than their counterparts (**Figure 6**). Similar results were observed in patients with distant CRC (**Figure 7**) or multiple primary tumors as well as in those who were not treated with surgery (**Figure 8**). The relationships between CVSM and race or tumor site are shown in **Figure 9** and **Figure 10**, respectively.

Conditional standardized mortality ratio

The comparative results of cSMR data between CRC patients and the general

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population are displayed in **Table 2**. Our study revealed that the CVSM and overall mortality in CRC patients were significantly higher than those in the general US population in all age subgroups. In the analysis of cSMR for CVSDs, our research discovered that younger CRC patients (age < 50 years) harbored the highest CVSM, which was 13 times higher than that of elderly patients aged 80-84 years (83.14, 95% CI: 69.99-97.42 *versus* 6.91, 95% CI: 6.66-7.17).

Cause-specific hazard ratios (HRs)

Multivariate analyses using a competing risk model showed that CVSM was positively correlated with age. The HRs were 3.098 (95% CI: 2.617-3.667), 6.666 (95% CI: 5.654-7.859), and 10.951 (95% CI: 9.299-12.897) for patients aged 55-64 years, 65-74 years, and ≥ 75 years old, respectively. However, the HRs for the patients who received radiotherapy or chemotherapy were 0.849 (95% CI: 0.783-0.921) and 0.653 (95% CI: 0.616-0.691), respectively, suggesting a protective effect for these factors against CVSM. Similar results were also observed in patients with multiple primary tumors (0.685, 95% CI: 0.659-0.712) and distant CRC (0.298, 95% CI: 0.149-0.598). By contrast, patients undergoing surgery faced a 1.558 times higher risk of CVSM than those who were not surgically treated. The connection between other individual prognostic factors and CVSM among CRC patients is displayed in **Table 3**.

Discussion

In this study, we analyzed the CVSM in a large registry-based CRC cohort and compared this outcome with that in the general population. We also characterized prognostic factors of CVSM in CRC patients. We found that the CVSM in CRC patients was significantly higher than that in the general population. Moreover, we identified several important clinical factors affecting CVSM in the patients. These data may provide a comprehensive understanding of CVSM in CRC and help guide risk stratification and therapeutic optimization for CVSDs in this population.

To date, this is the largest individual patient-level study to explore long-term CVSM

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among CRC patients. Our study revealed that the CVSM in CRC patients was increased compared to that in the general population, which was in line with previous studies claiming that malignant tumor lesions were associated with the development of CVSDs.[5, 16, 17] It is well known that the brain-gut axis is a bidirectional link between the brain and the gastrointestinal tract.[18] Published data have indicated that the gut microbiota, as an important component of the brain-gut axis, can contribute to CVSDs by mediating many pathways, including vascular inflammation, lipopolysaccharide signaling and endothelial and immune cell functions.[19-22] In addition, studies have demonstrated that abnormal vitamin K and trimethylamine N-oxide levels produced by gut microbiota can lead to several pathologies, including thrombosis, atherosclerosis and coagulopathy,[23-26] all of which are linked with an increased risk of CVSDs occurrence. Given that the gut microbiota is aberrant in CRC,[27-29] these data altogether suggest that the gut microbiota may play a pivotal role in CVSDs development among CRC patients. Future animal studies involving various gut microbiota models may be helpful in further clarifying this correlation and the potential mechanism between them.

Moreover, our study also found that age displayed a positive association with CVSDs in CRC, in agreement with previous studies.[12] This condition may likely be caused by the fact that older patients usually have worse elasticity of blood vessel walls than younger patients. In addition, elderly patients suffering from other comorbidities (such as hypertension and diabetes) may be prone to cerebrovascular accidents.[30] Notably, our analysis revealed that young CRC patients (< 50 years old) experienced a highest risk of CVSM than the general population, which may be caused by unhealthy dietary lifestyles and a lack of physical activity in these survivors.[31] Additionally, our data indicated that the year of diagnosis was negatively correlated with CVSM. This result may be attributed to the improved ability of diagnosis and treatment for CVSDs among CRC patients in recent years.[32]

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Interestingly, our data hinted that female CRC patients had a higher CVSM, which was contradictory to previous reports proving that estrogens provide a protective effect on vascular disease.[33, 34] This inconsistency may be because most female CRC patients are diagnosed at an older age when their ovarian function is remarkably compromised, thus decreasing estrogen production. Another major finding was that we found that both chemotherapy and radiotherapy favorably influenced the CVSM of CRC patients. Preceding observations have confirmed that the intensity of the immune response (specifically including the level of IFN-γ, as well as $CD4^+$ and $CD8^+$ cell densities) is positively associated with the development of CVSDs.[35, 36] Considering this, we speculate that CRC-associated treatments may affect CVSDs outcomes by regulating the inflammatory response, thus leading to a reduction in proinflammatory factors entering the blood-brain barrier. Besides, our study disclosed that CRC patients who underwent surgery had an increased risk of CVSM, in accordance with preceding data indicating that hemodynamic changes during the perioperative period may cause the thrombus to fall off, thereby leading to stroke in CRC patients.[37, 38] Another possible explanation for such an association is that surgical procedure especially in patients with advanced CRC may trigger tumor cells to release more proinflammatory factors entering the blood-brain barrier and therefore promote the occurrence of CVSDs.

Furthermore, our results showed that patients with multiple tumors had a lower CVSM than their counterparts. This phenomenon is easy to understand, as patients in this subgroup are more likely to receive relevant interventions for CVSDs, thereby resulting in a decreased CVSM rate. It has been described that circulating tumor cells and their extracellular vesicles could lead to CVSDs in patients with metastatic diseases by disrupting the blood-brain barrier and inducing inflammation-associated injuries of vascular endothelial cells.[39, 40] Inconsistent with this outcome, however, we uncovered that CRC patients harboring distant or metastatic entities experienced a reduced risk of CVSM. Patients with advanced CRC may die before the incidence of

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CVSDs because of the short survival time. Apart from this, it should be noted that the small number of patients assigned to the *in situ* CRC subtype could lower the statistical power and thus introduce bias to our outcome. Taken together, these data may provide an explanation for the inverse relationship between patients' CVSM and distant CRC.

Strengths and limitations

The strengths of this study are the large sample size, the stratified analyses by detailed clinicopathological variables and the long follow-up time. However, due to the limitation of data collection in the SEER database, we did not obtain information on the molecular features, type of chemotherapy or radiotherapy (specifically including therapeutic duration and dosage) or resection modality for our analysis, which may compromise the accuracy of our results. The same data restriction precludes us from performing further subgroup analysis stratified by the specific cause of CVSM in an attempt to produce more accurate data on cerebrovascular-specific events in CRC and the potential relationship between them. Finally, additional studies are required to further unveil the precise mechanism of how CVSM could be increased in CRC patients.

Conclusion

The present study analyzed the incidence of CVSM in CRC patients and systematically investigated the influencing factors associated with these events. We found that the CVSM of CRC patients was significantly higher than that of the general US population and identified several potential predictors of CVSM in the population. These data may be useful for the prevention, risk stratification and therapeutic optimization of CVSM in CRC patients. Further prospective studies involving large sample sizes with more complete clinical and molecular data are needed to confirm our current findings.

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Figure legends

Figure 1. Flowchart of the selection of study subjects.

Figure 2. Cumulative cause-specific mortality among colorectal cancer patients.

Figure 3. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by age.

Figure 4. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by year at diagnosis.

Figure 5. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by grade.

Figure 6. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by gender, chemotherapy and radiotherapy.

Figure 7. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by stage.

Figure 8. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by number of primary tumors and surgery.

Figure 9. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by race.

Figure 10. Cumulative cerebrovascular-specific and colorectal cancer-specific mortality stratified by tumor site.

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Table 1. Basic characteristics of included patients with colorectal cancer at time of diagnosis

Factors	Number of patients (%)
N	563298
Age (continuous, mean ± SD)	68.6 ± 13.1
Age (years, groups)	
< 50	47947 (8.5)
50-64	150201 (26.7)
65-74	158222 (28.1)
75+	206928 (36.7)
Year of diagnosis	
≤ 2000	269323 (47.8)
2001-2005	148725 (26.4)
2006-2015	145250 (25.8)
Sex	
Female	276592 (49.1)
Male	286706 (50.9)
Race	
White	469427 (83.3)
Black	53364 (9.5)
Other/ unknow	40507 (7.2)
Grading	
I	69849 (12.4)
II	375542 (66.7)
III	109875 (19.5)
IV	8032 (1.4)
Stage	
In situ	356 (0.1)
Localized	224781 (39.9)
Regional	234669 (41.7)
Distant	103492 (18.4)

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Tumor site	
Rectum	99924 (17.7)
Rectosigmoid junction	50683 (9.0)
Overlapping lesion or tumors	26848 (4.9)
Involving multiple locations	
Sigmoid colon	123198 (21.9)
Descending colon	24961 (4.4)
Splenic flexure of colon	14779 (2.6)
Transverse colon	36841 (6.5)
Hepatic flexure of colon	20629 (3.7)
Ascending colon	67767 (12.0)
Appendix	3987 (0.7)
Cecum	93681 (16.6)
Cause of death	
Alive	155753 (27.7)
Colorectal cancer	202872 (36.0)
Cerebrovascular-specific diseases	14600 (2.6)
Other cancer	46648 (8.3)
Other non-cancer diseases	143425 (25.5)
Radiotherapy	
Yes	65352 (11.6)
No/unknown	497946 (88.4)
Chemotherapy	
Yes	163975 (29.1)
No/unknown	399323 (70.9)
Number of primary tumors	
One	398107 (70.7)
Multiple	165191 (29.3)
Surgery	
Yes	530282 (94.1)
No	33016 (5.9)

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Table 2. Age-specific and overall standardized mortality ratios for the years 1999-2015 among colorectal cancer relative to the USA standard population

Group	cSMR cerebrovascular-specific	*P*-value	cSMR overall	*P*-value
Age[a]				
< 50	83.14 (69.99-97.42)	< 0.0001	371.66 (366.75-376.62)	< 0.0001
50-54	21.76 (18.81-24.92)	< 0.0001	97.64 (96.23-99.06)	< 0.0001
55-59	26.54 (24.20-29.00)	< 0.0001	76.96 (76.04-77.88)	< 0.0001
60-64	24.56 (22.96-26.22)	< 0.0001	58.68 (58.09-59.27)	< 0.0001
65-69	20.92 (19.88-21.99)	< 0.0001	43.20 (42.82-43.57)	< 0.0001
70-74	16.37 (15.72-17.04)	< 0.0001	30.66 (30.41-30.90)	< 0.0001
75-79	10.64 (10.26-11.03)	< 0.0001	20.80 (20.64-20.96)	< 0.0001
80-84	6.91 (6.66-7.17)	< 0.0001	13.58 (13.47-13.69)	< 0.0001

cSMR, conditional standardized mortality ratio.

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Table 3. Cause-specific hazard and 95% confidence intervals for cerebrovascular-related mortality among colorectal cancer patients

Factors	Number of patients	Cause-specific hazards ratios	
		Cerebrovascular	*P*-value
Age at diagnosis (years)			
< 50	47947	1.000 (ref.)	
50-64	150201	3.098 (2.617-3.667)	< **0.0001**
65-74	158222	6.666 (5.654-7.859)	< **0.0001**
≥ 75	206928	10.951 (9.299-12.897)	< **0.0001**
Sex			
Male	286706	1.000 (ref.)	
Female	276592	1.223 (1.183-1.264)	< **0.0001**
Surgery			
No	33016	1.000(ref.)	
Yes	530282	1.558 (1.385-1.754)	< **0.0001**
Radiotherapy			
No/unknown	497946	1.000 (ref.)	
Yes	65352	0.849 (0.783-0.921)	< **0.0001**
Chemotherapy			
No/unknown	399323	1.000 (ref.)	
Yes	163975	0.653 (0.616-0.691)	< **0.0001**
Year of diagnosis			
≤ 2000	269323	1.000 (ref.)	
2001-2005	148725	0.610 (0.586-0.636)	< **0.0001**
2006-2015	145250	0.451 (0.428-0.475)	< **0.0001**
Number of primary tumors			
One	398107	1.000 (ref.)	
Multiple	165191	0.685 (0.659-0.712)	< **0.0001**
Stage			
In situ	356	1.000 (ref.)	

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Localized	224781	1.361 (0.682-2.715)	0.3800
Regional	234669	1.120 (0.561-2.236)	0.7500
Distant	103492	0.298 (0.149-0.598)	**0.0006**
Grading			
I	69849	1.000 (ref.)	
II	375542	0.953 (0.910-0.998)	**0.0410**
III	109875	0.892 (0.840-0.946)	**0.0002**
IV	8032	1.023 (0.875-1.196)	0.7800
Race			
White	469427	1.000 (ref.)	
Black	53364	1.019 (0.958-1.085)	0.5500
Other/Unknow	40507	1.110 (1.039-1.186)	**0.0019**
Tumor site			
Cecum, appendix and ascending colon	165435	1.000 (ref.)	
Transverse colon and hepatic or splenic flexure of colon	72249	1.061 (1.008-1.116)	**0.0240**
Descending colon, sigmoid colon and rectosigmoid junction	198842	0.968 (0.930-1.008)	0.1200
Rectum	99924	0.900 (0.851-0.952)	**0.0002**
Overlapping lesion or tumors involving multiple locations	26848	1.057 (0.972-1.149)	0.1900

Bold values indicate $P < 0.05$.