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ORIGINAL ARTICLE

Risk factors for cardiovascular mortality in patients with colorectal cancer: a population-based study

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Abstract

Background Patients with colorectal cancer are at increased risk of cardiovascular mortality compared to the general population. The purpose of this study is to identify risk factors of cardiovascular mortality in patients with colorectal cancer.

Methods A retrospective review of the Surveillance Epidemiology and End Results (SEER) database was performed between 2010 and 2014. Standardized Mortality Ratios (SMRs) for cardiovascular mortality were calculated by comparing the number of expected deaths in the United States according to the National Center for Health Statistics (ICD-10 codes I00-I99) to the number of observed deaths in the database. Logistic regression was used to identify independent risk factors.

Results Overall, 164,719 patients were identified (mean age at diagnosis 67 ± 13.9 years, 52.7% males, 47.3% females), of which 4854 (2.9%) died from cardiovascular disease. The majority of cardiovascular deaths occurred during the first year after diagnosis (2658, 54.8%). SMRs for cardiovascular mortality were 11.7 (95% CI 11.3–12) among all patients, 12.1 (95% CI 11.7–12.6) for male patients and 11.1 (95% CI 10.6–11.6) for female patients, with SMRs being higher for younger patients. Older age, male sex, African–American race, elevated CEA and not undergoing curative surgery were independent risk factors of cardiovascular mortality in patients with colorectal cancer.

Conclusion Patients with colorectal cancer are associated with an increased risk of cardiovascular death, especially during the first year after diagnosis. Older age, male sex, African–American race, elevated CEA and not undergoing curative surgery are independent risk factors of cardiovascular death.

Keywords Colorectal cancer · Cardiovascular · Mortality

Introduction

Colorectal cancer (CRC) ranks third among the global causes of death due to cancer [1]. The incidence of CRC in North America has been estimated at 30.1 and 22.7 cases per 100,000 people every year for males and females, respectively, constituting 9.2–10% of all new cancer diagnoses worldwide [2]. A wide variety of risk factors—both of environmental and genetic concern—has been associated with the development of CRC, such as obesity, smoking and alcohol consumption [2]. In addition, consumption of red meat, low dietary fiber intake and diabetes mellitus have also been strongly associated with a higher risk for developing the disease [2]. The incidence of CRC also raises with advanced age and is higher among people of African–American race and patients with a positive family history [2]. The same risk factors are also associated with the development of cardiovascular disease [3, 4], and it has been suggested that there might be an overlap between the two patient populations [5]. In addition, a higher prevalence of cardiovascular risk factors in long-term survivors of CRC has been found in comparison to the general population [6].

The incidence of mortality from cardiovascular disease has increased by 14.5% between 2006 and 2016, with ischemic heart disease and cerebrovascular disease

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constituting 85.1% of these deaths [1]. Several cohort studies have identified an increased risk for cardiovascular disease and death in CRC survivors [7–9]. In addition, CRC survivors are more likely to die from their cancer during the first 5 years from diagnosis; however, for those who survive past the 8 years the likelihood of experiencing death from cardiovascular disease increases dramatically, surpassing the one from CRC itself [10]. Contemporary data indicate that there is a need to investigate cardiovascular mortality in patients with CRC due to the commonly long-term survival of this group and the underlying pathogenetic associations. Due to these factors, cardiovascular morbidity and mortality are expected to have a major impact on both survival and quality of life in CRC survivors. Screening recommendations for cardiovascular disease are needed and thus relevant risk factors must first be identified to determine groups in need of earlier screening and aggressive treatment. The purpose of this study is to examine the incidence of cardiovascular mortality in patients with CRC and identify risk factors of cardiovascular mortality.

Methods

A retrospective analysis of the Surveillance Epidemiology and End Results (SEER) database was performed to identify patients with colorectal carcinoma that were diagnosed between 2010 and 2014. The following ICD-O-3 histological codes were considered: 8140, 8141, 8143–8145, 8147, 8210, 8211, 8220, 8221, 8260–8263, 8480, 8481, and 8490. Patients with in situ tumors and those without a microscopic diagnosis were also excluded from the study. The following classifications in terms of cause of death were considered: diseases of heart, aortic aneurysm and dissection, atherosclerosis, cerebrovascular diseases, hypertension without heart disease and other diseases of arteries, arterioles, capillaries. The study was exempted from Institutional Review Board due to SEER's use of unidentifiable patient information.

Statistical analysis

Univariate and multivariable survival analysis was performed to identify independent predictors of cardiovascular mortality using the Cox proportional hazards model. Data for the incidence of cardiovascular mortality (ICD-10 codes I00-I99) in the general population were received from the National Center for Health Statistics for years 2010–2014. Standardized Mortality Ratios (SMRs) were then calculated as the ratios of the number of observed deaths divided by the number of expected deaths. The model's predictive ability was assessed using Harrell's c-index [11]. Two-tailed statistical tests were performed on SPSS v.24 (IBM Corp., Armonk, NY). The threshold of significance was set at 0.05.

Results

Overall, 164,719 patients were identified. Mean age at diagnosis was 67 ± 13.9 years. Males constituted 52.7% and females constituted 47.3% of the cohort. Median follow-up period for patients in the cohort was 18 months (95% CI 18–19 months). Among all patients, 4854 (2.9%) patients died due to cardiovascular causes, which was the second most common cause of death after cancer-specific mortality. Most cardiovascular deaths occurred during the first year after cancer diagnosis (2658, 54.8%). Detailed characteristics of the patient cohort are displayed at Table 1.

Comparison of cardiovascular mortality with the general population

The SMRs for cardiovascular mortality of patients with CRC compared to the general population were 11.7 (95% CI 11.3–12) in the entire cohort, 12.1 (95% CI 11.7–12.6) for males and 11.1 (95% CI 10.6–11.6) for females. SMRs for cardiovascular mortality were significantly increased compared to the general population for all age groups above 25 years of age, with differences between patients with CRC and the general population being more pronounced in younger age groups (Table 2).

Predictors of cardiovascular mortality

Univariate analysis identified older age ($p < 0.001$), male sex ($p < 0.001$), race ($p < 0.001$), tumor location ($p < 0.001$), greater primary tumor size ($p < 0.001$), higher tumor grade ($p = 0.001$), elevated CEA ($p < 0.001$), not undergoing surgery ($p < 0.001$), absence of nodal ($p < 0.001$) and distant metastasis ($p < 0.001$) to be associated with cardiovascular mortality. On multivariable analysis, older age (HR 1.09, 95% CI 1.09–1.1, $p < 0.001$), sex (female vs. male: HR 0.64, 95% CI 0.58–0.7, $p < 0.001$), race (African–American vs. white: HR 1.32, 95% CI 1.14–1.52, $p < 0.001$, other vs. white: HR 0.81, 95% CI 0.68–0.97, $p = 0.02$), elevated CEA (HR 1.43, 95% CI 1.31–1.57, $p < 0.001$) and curative surgery (HR 0.59, 95% CI 0.49–0.71, $p < 0.001$) were independent risk factors of cardiovascular mortality (Table 3). The model's discriminatory c-index was 0.93. Further analysis to identify separate risk factors for patients that died from cardiovascular causes during the first year after diagnosis again identified older age, male sex, African–American race, elevated CEA and not undergoing curative surgery as independent risk factors (Supplementary Table 1).

Table 1 Characteristics of the patient cohort

	N = 164,719
Age (years)	67 ± 13.9
Sex	
Male	86,849 (52.7%)
Female	77,870 (47.3%)
Race	
White	129,151 (78.4%)
Black	19,459 (11.8%)
Other	14,822 (9%)
Cause of death	
Cancer-specific mortality	32,379 (19.7%)
Cardiovascular	4854 (2.9%)
Pulmonary	1999 (1.2%)
Other malignancy	1346 (0.8%)
Septicemia	405 (0.2%)
Diabetes mellitus	381 (0.2%)
Timing of cardiovascular death	
1st year	2658 (54.8%)
2nd year	993 (20.5%)
3rd year	674 (13.9%)
4th year	385 (7.9%)
5th year	144 (3%)
Tumor location	
Right colon	57,539 (34.9%)
Left colon	44,215 (26.8%)
Transverse colon	11,654 (7.1%)
Rectum	34,008 (20.6%)
Rectosigmoid	12,777 (7.8%)
Tumor grade	
WD	13,569 (8.2%)
MD	104,968 (63.7%)
PD/UD	26,616 (16.2%)
Primary tumor size (cm)	4.6 ± 3.8
CEA	
Normal	47,604 (28.9%)
Borderline	497 (0.3%)
High	44,200 (26.8%)
Perineural invasion	13,276 (8.1%)
T stage	
T1	28,761 (17.5%)
T2	19,979 (12.1%)
T3	71,943 (43.7%)
T4	24,405 (14.8%)
Nodal metastasis	59,769 (36.3%)
Distant metastasis	31,640 (19.2%)
Surgery	
Performed	145,441 (83.8%)
Not performed	26,425 (15.2%)

WD well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *CEA* carcinoembryonic antigen

Discussion

The results of this study demonstrate that patients with CRC have a significantly higher risk of cardiovascular death compared to the general population that is more pronounced for younger cancer survivors. Older age, male sex, African–American race and elevated CEA are independent predictors of cardiovascular mortality in patients with CRC. These results should be considered when assessing the individual cardiovascular risk in CRC survivors and serve as an indication for more rigorous diagnostic testing and risk factor modification (e.g., tighter glycemic control, tighter blood pressure control), especially during the first year after diagnosis.

As we previously mentioned, CRC and cardiovascular disease are two conditions that often coexist, since the risk profiles for the development of the two diseases are similar. Obesity and cigarette smoking are lifestyle-related risk factors strongly correlated both with colorectal neoplasia and cardiovascular disease. Inflammatory mediators produced by excessive visceral fat and tobacco derived carcinogens promote the development of CRC [12], whereas polyunsaturated fatty acids and tobacco smoke induce oxidative stress and endothelial dysfunction by generating free radicals [13, 14]. Therefore, a common pathophysiology between CRC and cardiovascular disease could possibly explain the higher prevalence of cardiovascular disease among CRC patients as well as the increased probability of cardiovascular death in this group. Several cohort studies have demonstrated an elevated risk of cardiovascular death in CRC survivors [7–9, 15, 16], including studies using the SEER database. However, these studies included patients from previous eras, where the management for both CRC and cardiovascular disease was vastly different, while another study focused exclusively on young adults [15]. In this study, we included only recently diagnosed patients to better reflect current treatment paradigms. Previous studies had also not identified any relevant risk factors nor explored the timing of cardiovascular death.

Improvements in cancer treatment and care over the past few decades have resulted in an increase in life expectancy of patients diagnosed with CRC. As patients live longer and mortality rates due to cancer decrease, it is expected that other causes of death will become more prevalent, with cardiovascular disease accounting for the majority of non-cancer deaths. However, the majority of cardiovascular deaths in this study occurred during the 1st year after diagnosis, although previous findings have confirmed that the risk of cardiovascular death remains elevated compared to the general population beyond 12 months and even rises afterwards [16]. A separate analysis did not reveal any additional risk factors for cardiovascular mortality during

Table 2 Standardized mortality ratios (SMRs) for cardiovascular mortality by age and sex

	SMR	(95% CI)	Incidence per 100,000 people 95% (CI)	Expected deaths	Number of patients	Observed deaths
Total	11.7	11.3–12	252.6 (252.4–252.9)	416.08	164,719	4854
Male	12.1	11.7–12.6	255.9 (255.5–256.2)	222.25	86,849	2700
Female	11.1	10.6–11.6	249.5 (249.1–249.8)	194.29	77,870	2154
1st year	6.4	6.1–6.6	252.6 (252.4–252.9)	416.08	164,719	2658
2nd year	3.6	3.4–3.8	252.6 (252.4–252.9)	277.6	109,914	993
3rd year	3.7	3.4–4	252.6 (252.4–252.9)	183.4	72,624	674
4th year	3.5	3.2–3.9	252.6 (252.4–252.9)	108.9	43,094	385
5th year	2.9	2.5–3.4	252.6 (252.4–252.9)	49.1	19,450	144
5–14 years	–	–	0.7 (0.7–0.7)	0	6	0
Male	–	–	0.7 (0.7–0.8)	0	4	0
Female	–	–	0.7 (0.6–0.7)	0	2	0
15–24 years	–	–	2.9 (2.8–3)	0	176	0
Male	–	–	3.7 (3.6–3.8)	0	106	0
Female	–	–	2 (2–2.1)	0	70	0
25–34 years	13	1.1–37.9	10 (9.8–10.1)	0.2	1536	2
Male	–	–	13 (12.8–13.2)	0.1	823	0
Female	40.7	3.5–118.5	6.9 (6.7–7.1)	0.05	713	2
35–44 years	10.6	6.5–15.8	33 (32.8–33.3)	2	5977	21
Male	10.2	5.5–16.4	44.2 (43.8–44.6)	1.4	3110	14
Female	11.1	4.3–21.2	21.9 (21.6–22.2)	0.6	2867	7
45–54 years	3.7	2.9–4.6	100.3 (99.9–100.7)	21.5	21,443	80
Male	3.4	2.5–4.3	139.2 (138.5–139.9)	16.3	11,720	55
Female	4.1	2.6–5.9	62.5 (62.1–63)	6.1	9723	25
55–64 years	4.7	4.3–5.2	230.4 (229.7–231.1)	88.2	38,265	418
Male	4.1	3.6–4.6	323.5 (322.4–324.7)	71.4	22,075	291
Female	5.5	4.5–6.5	143.6 (142.9–144.4)	23.2	16,190	127
65–74 years	4.3	4–4.5	508.2 (506.9–509.5)	230.1	45,271	982
Male	3.8	3.5–4.1	668 (665.9–670.2)	171.1	25,609	656
Female	4.5	4–5	368.3 (366.8–369.8)	72.4	19,662	326
75–84 years	2.8	2.7–3	1501.9 (1498.9–1504.8)	617.9	41,138	1744
Male	2.7	2.5–2.8	1808.9 (1804–1813.9)	372.9	20,617	997
Female	2.9	2.7–3.1	1274.5 (1270.9–1278.1)	261.5	20,521	747
85+ years	1.4	1.4–1.5	5420.7 (5412.3–5429.1)	1356.2	25,018	1956
Male	1.5	1.4–1.6	5834.9 (5819.8–5850.1)	598.9	10,264	882
Female	1.4	1.3–1.5	5212.8 (5202.6–5222.9)	769.1	14,754	1074

SMR standardized mortality ratio, *CI* confidence interval

the first year after diagnosis. The observed increase in cardiovascular mortality during the first year after diagnosis in patients with CRC could potentially be explained by the extensive use of potentially cardiotoxic chemotherapeutic agents. Several of the currently used chemotherapeutic drugs for the treatment of CRC, such as 5-fluorouracil and bevacizumab, exhibit a cardiotoxic potential which may contribute to the progressive decline of cardiovascular function and eventually lead to premature cardiovascular death [17, 18]. Chemotherapy data are unfortunately not available in the SEER database and therefore we cannot reach specific conclusions with regards to the contribution of specific chemotherapy regimens to cardiovascular mortality. However, non-operative management was an independent risk factor for cardiovascular death and these patients likely received chemotherapy with the potentially cardiotoxic FOLFOX/FOLFIRI ± bevacizumab regimens per NCCN guidelines [19, 20], which might have contributed to the increased risk of cardiovascular death in the non-operative group. Comparing the SMRs of cardiovascular death in the study population to previous SEER analyses among patients diagnosed in previous decades

Table 3 Univariate and multivariable analysis for predictors of cardiovascular mortality in colorectal cancer patients

	Univariate		Multivariable	
	HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Age	1.09 (1.08–1.09)	< 0.001	1.09 (1.085–1.094)	< 0.001
Sex		< 0.001		< 0.001
Male	Ref		Ref	
Female	0.89 (0.84–0.94)		0.65 (0.59–0.71)	
Race		< 0.001		< 0.001
White	Ref		Ref	
Black	1.06 (0.98–1.16)	0.167	1.31 (1.13–1.52)	< 0.001
Other	0.69 (0.61–0.77)	< 0.001	0.81 (0.68–0.97)	0.021
Tumor location		< 0.001		0.495
Right colon	Ref		Ref	
Left colon	0.77 (0.71–0.82)	< 0.001	1.08 (0.96–1.21)	0.225
Transverse colon	1.14 (1.02–1.26)	0.017	1.14 (0.97–1.34)	0.102
Rectum	0.7 (0.65–0.76)	< 0.001	1.04 (0.9–1.2)	0.624
Rectosigmoid	0.66 (0.59–0.75)	< 0.001	1.05 (0.87–1.28)	0.605
Tumor size	1.001 (1.001–1.002)	< 0.001	1 (1–1.001)	0.69
Tumor grade		0.001		0.035
WD	Ref		Ref	
MD	1 (0.9–1.1)	0.948	0.84 (0.72–0.99)	0.037
PD/UD	1.16 (1.03–1.3)	0.017	0.94 (0.78–1.13)	0.499
CEA		< 0.001		< 0.001
Normal	Ref		Ref	
Borderline	1.54 (0.96–2.45)	0.071	0.9 (0.47–1.74)	0.758
High	1.44 (1.33–1.56)	< 0.001	1.42 (1.29–1.55)	< 0.001
Perineural invasion	0.94 (0.83–1.05)	0.273		
T stage		0.074		
T1	Ref			
T2	0.99 (0.89–1.09)	0.83		
T3	0.91 (0.84–0.9)	0.025		
T4	0.98 (0.88–1.09)	0.684		
Nodal metastasis	0.77 (0.72–0.82)	< 0.001	0.99 (0.89–1.09)	0.797
Distant metastasis	0.82 (0.75–0.89)	< 0.001	1.03 (0.88–1.2)	0.739
Curative surgery		< 0.001		< 0.001
Not performed	Ref		Ref	
Performed	0.41 (0.38–0.44)		0.59 (0.49–0.71)	

HR hazard ratio, *CI* confidence interval, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *CEA* carcinoembryonic antigen

shows that the incidence of cardiovascular death has not changed considerably (e.g., 1st year: SMR 6 vs. 6.4, 2nd year SMR: 3.5 vs. 3.6, 3rd year SMR 3.5 vs. 3.7) despite the advances in cardiovascular care [16]. This observation also underlies the need to improve cardiovascular care and prevention in these patients. It also shows that novel chemotherapeutic agents have not had a significant impact on cardiovascular mortality.

In an attempt to predict CRC patients at higher risk for cardiovascular mortality, we have identified older age, male sex, African–American race and elevated CEA levels as independent risk factors. Expectedly, cardiovascular disease is more prevalent among the elderly compared to younger patients with CRC. As age advances, patients tend to be accompanied by several comorbidities and have more compromised cardiovascular function combined with less physiological reserves. This may result in a higher ASA (American Society of Anesthesiologists) physical status classification, which may lead to a higher risk of perioperative cardiovascular death (e.g., perioperative myocardial infarction), a longer postoperative recovery and a lower threshold for cardiac decompensation after receiving cytotoxic chemotherapy. These may also explain why the majority of cardiovascular deaths occurred during the first year

after diagnosis, where both physical stress (due to aggressive treatment with chemotherapy or surgery) and emotional stress (due to cancer diagnosis) are higher. The above observations may also be attributed to the thrombophilic state that is associated with both malignancy and the postoperative state, potentially leading in turn to a higher propensity for coronary vascular thrombosis. Statistical analysis of epidemiological data demonstrate fluctuation in cardiovascular mortality according to sex and ethnicity, being higher among individuals of male sex and African–American ancestry. Results from previous studies show that females are more resilient to oxidative stress than males by hypothesizing a protective role of estrogens in pre-menopausal women, as well as by displaying differences in the expression of antioxidant enzymes [21]. In addition, male and African–American adults were less probable to meet a certain number of criteria for ideal cardiovascular health as opposed to females and other ethnicities, depicting lower levels of awareness and a debilitating effect of socioeconomic factors on cardiovascular health, respectively [22]. African–American patients are also disproportionately affected by hypertension, diabetes, and obesity [23]. By speculating that the current trend for increased cardiovascular mortality remains unchanged for CRC patients belonging in the above groups, male sex and African–American race could be considered risk factors for cardiovascular mortality in CRC patients. Serum CEA levels are widely used as a diagnostic tool for CRC [24]. A prognostic value of CEA has also been established by several studies demonstrating that higher levels of CEA in patients with stages II or III disease are linked to poorer survival outcomes, integrating CEA serum measurements in the surveillance of CRC patients [24]. It is possible that CRC patients presenting with higher CEA levels suffer from an overwhelming disease burden leading to greater cardiovascular decompensation from more aggressive treatment, therefore serving as a predictor of cardiovascular mortality. To our knowledge, there have been few studies attempting to correlate blood CEA levels with the stage of the disease, but had little success providing strong evidence of a more advanced disease in patients with higher values of CEA reflecting the need for further research in this field [25]. Although moderately differentiated tumor grade was associated with a significantly lower risk by multivariate analysis, we considered this finding to be a type I error, since the inverse relationship was observed by univariate analysis (i.e., higher grade associated with higher risk), while poorly differentiated/undifferentiated tumor grade was not associated with a significantly different risk of cardiovascular death by multivariate analysis.

The results of this study demonstrate that specific steps may be taken to identify CRC survivors at risk for cardiovascular death. Several validated risk assessment tools exist to measure the estimated risk of cardiovascular events in the general population, such as the Framingham risk score that includes several risk factors identified in this study (i.e., age, male sex) [26]. Such scores help clinicians stratify patients in low-, intermediate- and high-risk categories and these designations indicate the appropriate diagnostic testing that is required. The results of the present study indicate that all CRC survivors that were previously classified as low-risk according to these risk assessment tools and that required no additional testing according to the latest guidelines [27], should be upstaged to a higher risk category and undergo appropriate testing (e.g., exercise stress testing or coronary angiography) for diagnosing cardiovascular disease. The presence of additional risk factors, such as African–American race, elevated CEA or not undergoing cancer-directed surgery, should particularly alert clinicians for the elevated risk of cardiovascular death and prompt the timely implementation of appropriate diagnostic testing and control of modifiable risk factors, such as hypertension and diabetes. It should be noted that cardiovascular diagnostic testing should be performed early after diagnosis, since 54.8% of deaths occurred within the first year after diagnosis. At the moment, there are no recommendations for cardiovascular risk assessment in CRC survivors and the results of this study indicate that appropriate recommendations could be established.

A review of the literature on cardiovascular mortality among cancer patients reveals discrepancies between results, depending on their origin. In comparison with other recently conducted studies [16], the current study is designed with a shorter follow-up period, due to its focus on the identification of independent risk factors for cardiovascular mortality rather than focusing on the epidemiology of cardiovascular disease in the same group of patients. Furthermore, by including patients diagnosed after 2010, our study reflects the contemporary treatment paradigms for both CRC and cardiovascular disease, compared to previous studies that include patients that were diagnosed in earlier decades, while at the same time enabling a better estimation of disease-specific cardiovascular mortality rates as incidences closer to diagnosis are more likely to be related with CRC.

This study is limited by a retrospective design and the use of a multi-institutional database. These databases often include patients from different institutions that undergo different care. However, they also provide a large sample size and thus may accurately be employed to identify independent risk factors. The lack of data regarding prior cardiovascular disease or risk factors for cardiovascular death (e.g., diabetes mellitus, dyslipidemia etc.) is another limitation of the study. A relatively short follow-up period may be attributed to the inclusion of patients diagnosed after 2010, but this choice was made to better reflect contemporary treatment approaches, the latter of which have witnessed a meteoric evolution in the last 20 years alone.

In conclusion, patients with CRC were found to have an increased risk of cardiovascular mortality compared to the general population, similar to findings from previous smaller studies. In addition, older age, male sex, African–American race and elevated CEA were independent predictors of cardiovascular mortality. These results suggest that CRC patients should be screened early after diagnosis for cardiovascular disease and undergo tighter control of modifiable risk factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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